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Spectroscopic Evidence of a Free-Radical Mechanism in the Reduction of Schiff Bases by Formic Acid

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Abstract: The unprecedented direct detection of the free radical intermediate **7** in the reduction of Schiff bases **2** to the corresponding amines by formic acid using the EPR technique is reported. Monitoring the same reaction by NMR, line broadenings and signal shifts are observed, while the further evolution to products is triggered off by heating. No product formation or line broadening/shifts of the imine derivatives take place upon addition of the isoamyl nitrite spin trapper, which interrupts the chain process capturing the free radical **7**. Single electron species have also been detected in the similar reduction of the benzylidene-bis-piperidine **11** by formic acid.

INTRODUCTION

Formic acid, or its functional derivatives, can be used as reducing agent to obtain substituted amines from carbonyl- and amine- derivatives.[1] In particular, Schiff bases are transformed into the corresponding amines by formic acid. An azomethine reduction of this type is involved as the key step in the synthetically important reductive alkylation of ammonia and amines by aldehydes and ketones in the presence of formic acid (Wallach reaction).[2] When ammonium (or amine) salts of formic acid, or formamides, are used as reducing agents, the method takes the name of Leuckart reaction,[3] and the products are often N-formyl derivatives, rather than amines.[4] When primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is known as the Eschweiler-Clarke procedure.[5,6] The formic acid reduction of alkaloidal enamines or cyclic ketones is also noteworthy, in that it occurs in a highly stereospecific fashion.[7]

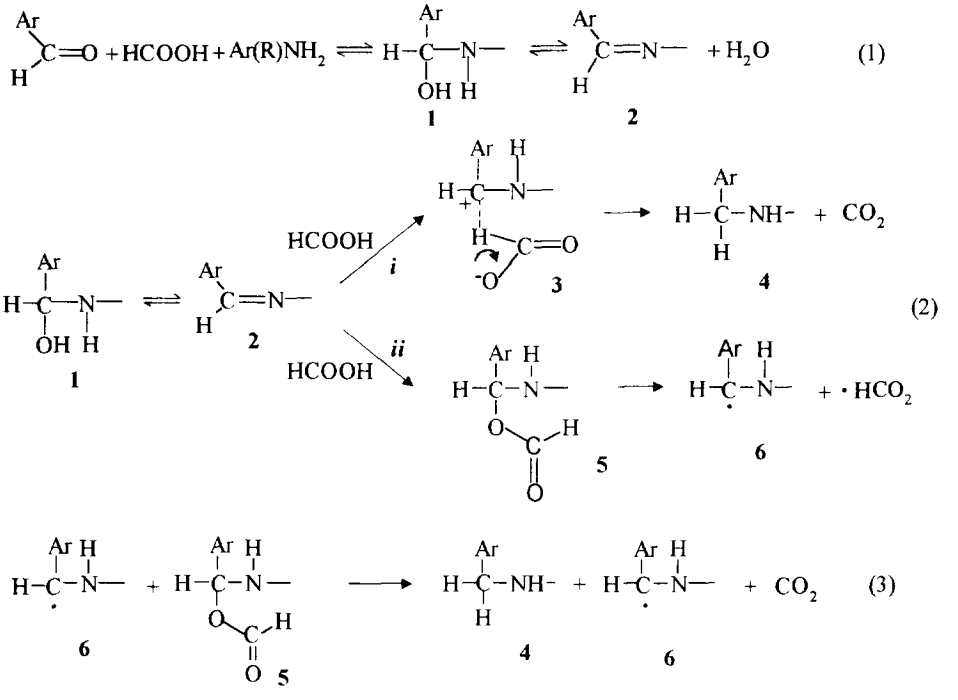
The formic acid synthetic route to substituted amines displays some advantages even after the advent of complex hydride reducing agents, the reagents (formic acid, or its derivatives) being cheap and the experimental procedure straightforward. The disavantages deal mainly with the poor yields,[3] due to the high sensitivity of the envisaged intermediate Schiff bases, or imines, to hydrolysis even in the presence of traces of water. However, preparatively useful conditions leading to nearly 90% yield have recently been developed.[8]

Despite the extensive synthetic utility of these reactions, the reaction mechanism has received only limited critical attention. Different reaction mechanisms have been suggested in scattered reports over the years. The initial formation of a carbinolamine derivative of type **1** (reaction 1 of Scheme 1) formed from the carbonyl compound reacting with a primary amine and formic acid, or directly with formamide, or as the result of the direct addition of formic acid to an imine, receives general agreement. For the subsequent evolution of species **1** to product **4** (reaction 2) two different hypotheses have been proposed: a widely accepted path

consists in a hydride translocation in the reduction step between the carbonium cation **3**, derived either from the imine **2** or from the α-aminoalcohol **1**, and a formate anion (path *i*);[9,10] an alternative path involves a homolytic cleavage of the corresponding carbinolamine formic ester **5** formed by nucleophilic addition of formate ion to the iminium derivative (path *ii*).[11] The product of this cleavage was assumed to consist of the free radical **6**, evolving to product **4** through the chain reaction 3.

Here we report on the detection of free radical species in the reduction of Schiff bases with formic acid in chloroform, providing an unprecedented direct spectroscopic demonstration of their intermediacy in these reactions.

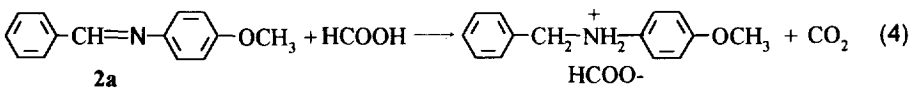
Scheme 1



RESULTS AND DISCUSSION

EPR detection of a radical intermediate in the reduction of Schiff bases by formic acid.

The reduction of Schiff bases to amines using formic acid is a well known reaction, as pointed out above. The interest in this reaction derives also from the general agreement on the intermediacy of Schiff bases in the methylation of arylamines by reaction with formaldehyde in the presence of formic acid.[12]



To ascertain the ionic or radical nature of this process, the reaction of 0.3 M **2a** with 1.4 M formic acid was monitored in degased, dried, and oxygen-free chloroform. The starting temperature in the EPR cavity was 200 °K, and the sample was then slowly warmed up to 293 °K. At this temperature the EPR spectrum *a* reported in Figure 1 was detected, and its intensity decreased slowly after the temperature in the cavity reached 318 °K. The computed spectrum (*b*, Figure 1),[13] converged to the following final fitting parameters, ascribable to a single radical species: A_N = 2.38 G, A_H = 5.86 G (2 H), A_H = 4.32 G (1 H); A_H = 5.25 G (1 H); A_H = 6.20 G (1 H); A_H = 1.12 G (2 H); the Lorentzian contribution to the lineshape was 82 % and the linewidth 1.04 G. These values are indicative of a delocalization of the unpaired electron on the aromatic rings, even taking into account that couplings lower than 1 G (the computed linewidth) escaped direct detection. This evidence is in agreement with structure 7, where hyperfine couplings around 4 - 6 G can be properly attributed to *ortho* and *para* phenyl hydrogens, and to the two non aromatic protons. On the other hand, also structure **8**, eventually obtained through the exchange reaction 5 between 7 and the formyl ester of type **5**, might meet the fitted coupling pattern.

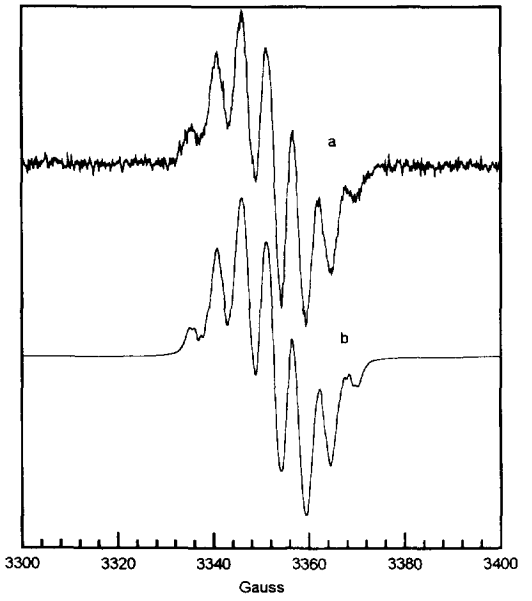
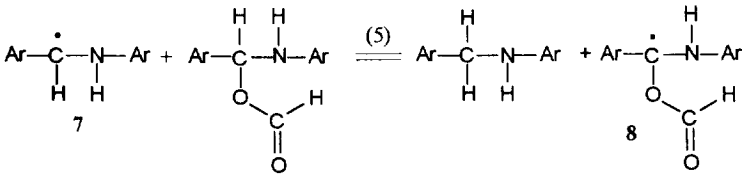


Figure 1. Experimental (a) and fitted (b) EPR spectra for the reaction of **2a** with formic acid in chloroform, assigned to radical **7**.



Since, in principle, a nitroxide free electron species could also explain the fitted hyperfine couplings, Schiff base **2a** was subjected to an oxidation reaction by the W(VI) peroxo polyoxo complex WO_5-PIC[14] in chloroform (6). The registered EPR spectrum, shown in Figure 2*a*, accounts for the expected nitroxide derivative **9** (then evolving to the corresponding nitrone), as shown by the fitted spectrum 2*b* (A_N = 9.95 G, A_H = 3.29 G (2H), and A_H = 2.40 G (2H)). On comparing Figures 1 with 2, the occurrence of a nitroxide species in the reduction of imines with formic acid can be definitely ruled out.

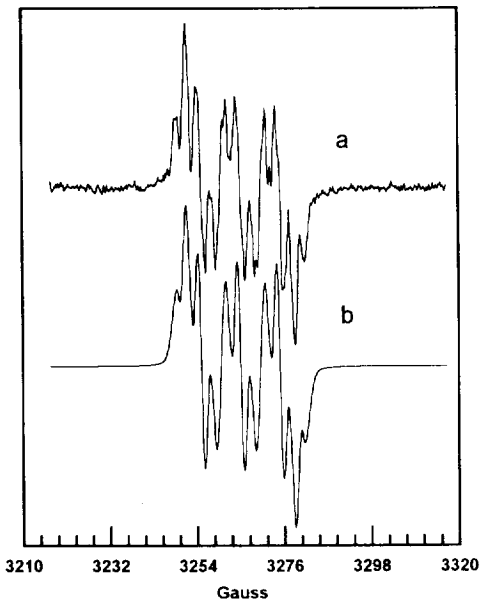
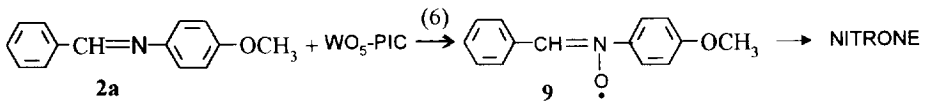


Figure 2. Experimental (a) and fitted (b) EPR spectra for the reaction of **2a** with WO_5-PIC, assigned to **9**.



NMR evidence of a radical intermediate in the reduction of Schiff bases with formic acid.

The reaction of benzyliden-4-methoxyaniline **2a** with formic acid in chloroform was also followed by ^1H NMR. As shown in Figure 3, on addition of a three- to tenfold excess of formic acid at room temperature, the spectrum of the starting Schiff base (*a*) underwent two evident changes (*b*): (*i*) a broadening of all the lines, most evident for the aromatic aniline derivative ring, the benzylic, and the methoxy protons; (*ii*) a small (0.1 -

0.2 ppm) downfield shift of some of the lines. Even after several hours, no further changes were observed in the spectrum, nor peaks ascribable to the expected reaction product were detected.

After the temperature was raised up to 318 °K, a singlet at 4.4 ppm, corresponding to the benzylic protons of the reaction product benzyl-p-methoxyaniline-HCOOH appeared (*c*), and increased slowly with time. Here, in addition to the peaks relative to the secondary aniline adduct, signals attributable to the hydrolysis products, benzaldehyde and the formic salt of *p*-methoxyaniline, were evident when rigorous anhydrous conditions were not achieved. Under these circumstances, the reaction yield decreased considerably. Finally, in spectrum *c* line broadenings were significantly reduced, and upfield shifts with respect to spectrum *b* were observed, indicating a depletion of radical **7** in favour of the reaction product.

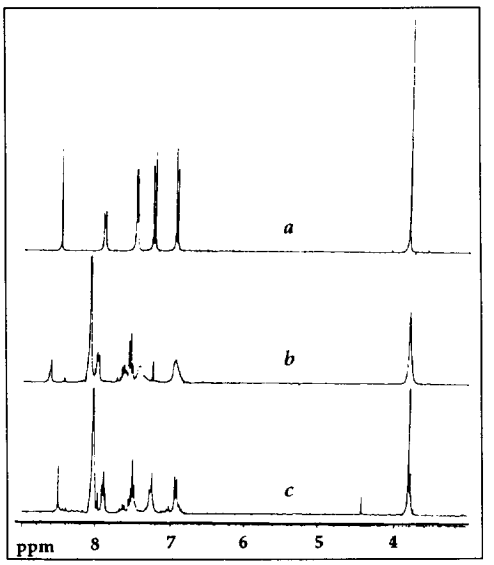
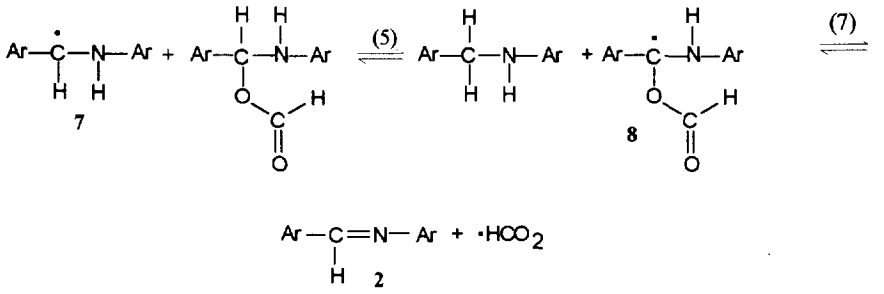


Figure 3. ^{1}H NMR spectra for the reaction of **2a** with formic acid in chloroform-*d*: *a*, spectrum of **2a**; *b*, after addition of formic acid at room temperature; *c*, reaction mixture heated at 45 °C.

The same behaviour was also observed with differently *p*-substitued Schiff bases **2b, 2c, 2d** (see experimental), and in the similar reaction of heteroaryl imine **2e** with formic acid. In all cases, line broadenings and signal shifts took place to a variable extent, the main difference being the rate of product formation once the reaction mixtures were heated.

It is important to point out that Figure 3 (b and c) does not represent the NMR spectrum of a radical, but the effects played by free radical species on the starting imine. Since these effects (broadenings and shifts) are not the same for all the peaks, in addition to a susceptibility effect due to the radical species, an exchange (equilibria 5 and 7) between the Schiff base **2** and free radical **7**, although very limited and not influencing the bulk of the reaction, can be reasonably proposed.



This exchange is probably sufficiently fast so that the peaks are in a weighted average position with respect to those relative to the imine and the radical species; the observed shifts are small with respect to the unreacted imine signals, indicating a very low concentration of the radical intermediate.[15]

With the aim to exclude an acid/base exchange, which in principle could give rise to the observed phenomena upon addition of formic acid, the reaction of imine **2a** was also carried out with glacial acetic acid and with chloroacetic acid, having respectively higher and lower pKa values (4.76 and 2.86, respectively) than that (pKa = 3.77) of formic acid.[16] No broadenings nor shifts were observed in both cases. Therefore, the phenomena reported in Figure 3 can be ascribed to the presence of radical species, in agreement with the evidence obtained through the EPR experiment reported for the same reaction.

Addition of a spin trapper to the reaction mixtures

A further unambiguous evidence in favour of the radical mechanism proposed for the HCOOH imine reduction was obtained by repeating the spectroscopic measurements in the presence of the free-radical scavenger isoamylnitrite.[17] The reaction of **2a** with formic acid in chloroform, upon addition of a fivefold excess of isoamyl nitrite with respect to the imine concentration, was therefore monitored by EPR. At 293 °K a signal appeared (Fig. 4), whose intensity increased with time up to a maximum, and then remained unchanged for days. This spectrum is different from that registered for the same reaction in the absence of the spin trapper (Fig 1a) and, on the basis of the computed spectral parameters (A_N = 8.29 G, A_H = 3.46 G), accounts for the single electron species **10**. The incursion of this radical, which fully replaces species 7 in the presence of isoamyl nitrite, provides a striking evidence that the spin trapper stops the chain process 3 capturing the radical 7, probably through the fast reaction 8.

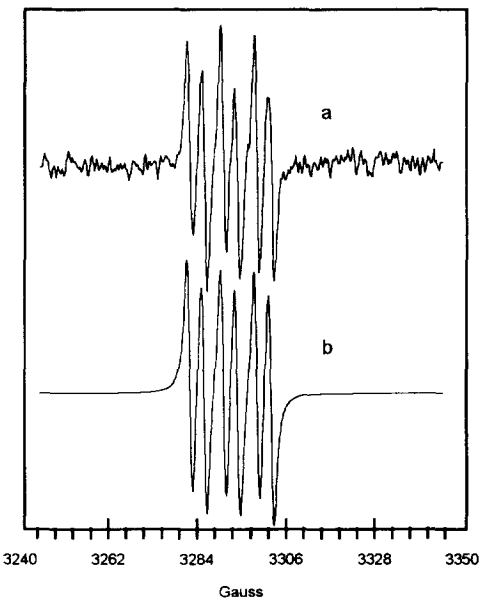
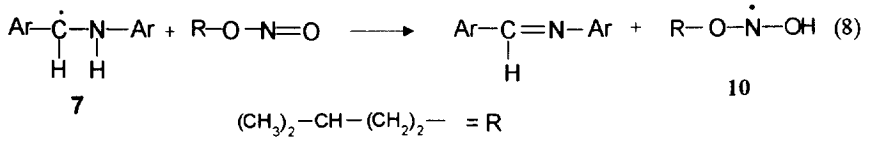


Figure 4. Experimental (a) and fitted (b) EPR spectra for the reaction of **2a** with formic acid in chloroform , in the presence of isoamyl nitrite (assigned to radical **10**).

The reaction of **2a** with formic acid in the presence of the fivefold excess of the spin trapper was also followed by NMR. Two main effects were observed: *i*) neither line broadenings, nor shifts were registered, whereas peaks relative to the scavenger suffered upfield shifts, and also underwent a splitting, due to the dimerization equilibrium, typical of nitroxide radicals;[18] *ii*) when the temperature was raised to 318°K and maintained for 2 hrs, no product signal appeared. This result afforded a conclusive support in favour of the radical nature of the title reaction.



Finally, all these reactions were also checked by TLC analyses of the reaction mixtures in ethyl acetate/chloroform (1/3, v/v) together with authentic imine and reduced amine samples. These results were in excellent agreement with those of the spectroscopic experiments, exhibiting the formation of the product with a kinetic trend parallel to that found by NMR, while no product formation occurred upon addition of the spin trapper to the reaction mixtures.

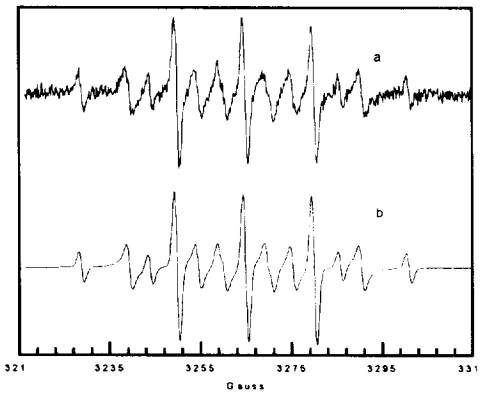
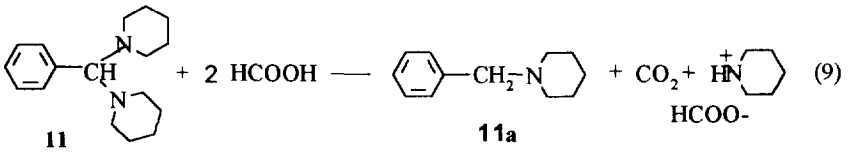


Figure 5. Experimental (a) and simulated (b) spectra for reaction 9.

Lukasiewicz's reaction.

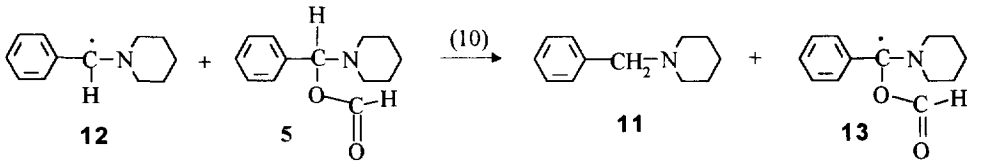
An extension of the general validity of the above demonstration in favour of a radical path in the Schiff bases reduction by formic acid is represented by the well known reaction of benzylidene-bis-piperidine **11** with formic acid.[11] This reaction (9) leads to the formation of the tertiary amine in good yield. Indirect evidence in favour of a free-radical process consisted mainly on the relevant inhibition/acceleration produced by addition of free radical scavengers/promoters in the reaction medium.

The reaction between 0.24 M **7** and 0.87 M anhydrous formic acid both in oxygen-free chloroform solution was carried out in the EPR cavity. When the temperature was raised from the initial value of 200 °K up to 298 °K, the spectrum reported in Figure 5 was observed. On the basis of fitted spectral parameters, the main contribution to the overall signal seems to be attributable to species **13**.



11 **11a**

The free radical **12**, proposed by Lukasiewicz, apparently was not directly found. However, his reaction scheme seems on the whole correct, but some variance is likely to be included. The eventually formed free-radical **12** could escape to the detection because of its further evolution, sufficiently fast, to the more stable radical species **13,** and the product, by reaction with the intermediate formic ester of type **5** (10).



12 **5** **11** **13**

This reaction is not in contrast with chain path 3, but represents a parallel depletion route of the intermediate **12**. The difference between the two reactions 3 and 5 consists in the hydrogen atom captured by radical **12**: the benzylic hydrogen could well compete with the formic hydrogen, also considering that the latter could be involved in a hydrogen bonding to the piperidine nitrogen to form a stable 5-membered ring.

Eventually, species **13** could evolve to species **12**, with CO_2 release.

CONCLUSIONS

The occurrence of a radical intermediate in the reaction of Schiff bases **2a-d** with formic acid, and also in the similar reaction of compound **2e**, is established, accounting for the formation of the final substituted amine or aniline derivatives. EPR experiments indicate the presence of radical intermediates, and allow the determination of their structure. NMR experiments are consistent with the formation of the radical species **7**, which at room temperature undergoes equilibration with the starting Schiff base. When a threshold temperature is reached, reaction 3 of Scheme 1 takes place at a low rate, due to the limited concentration of species **5** and **6** in the reaction medium. On the contrary, when the reaction is carried out with the addition of isoamyl nitrite spin trapper, no reduction product is detected, and NMR and EPR spectra reveal that the intermediate free radical species undergoes a fast exchange reaction with the isoamyl nytrite.

A similar radical path is also apparent in the aryl-alkyl derivative benzyliden-bis-piperidine, in which a free radical intermediate, detected by EPR , provided direct evidence to Lukasiewicz's mechanism.[11]

The intermolecular hydride transfer, already excluded in the well known Cannizzaro reaction in favour of a radical mechanism,[19] can be ruled out also in the present case. The proposed mechanism appears to have a general validity for all the reactions of carbonyl and amine compounds with formic acid and, eventually, their derivatives.

EXPERIMENTAL

ACS Chloroform, stabilized with ethanol, and chloroform-*d* were purchased from Aldrich and used as such. Formic acid was dehydrated by refluxing for 6 hours with phtalic anhydride and collecting the fraction distilling at 101°C.[20] Melting points are uncorrected.

Synthesis of imines. A solution of the aldehyde and of the amine (equimolar amounts, 10 mmol), was refluxed in 10 ml of dry ethanol. The time required varied from 15 min to 8 h , depending upon the basicity of the amine. The solvent was evaporated under reduced pressure and the composition of the residue was examined by TLC. The crude imines thus obtained were crystalline and in some cases, due to their low stabilities, were not purified before reduction. Mixtures of $CHCl_3$/petroleum ether (bp 40-70°C) were used as crystallization solvent.

Benzyliden-4-OCH_3-aniline, 2a : Yield 70%. Time 2 h. mp 73°C (lit. mp 72°C);[21]

(4-OCH_3- benzylidene)aniline, 2b: Yield 85%. Time 15 min. mp 63°C (lit. mp 63°C);[22]

Benzyliden-4-Cl-aniline, 2c: Yield 65%. Time 1 h. mp 62°C (lit. mp 62-3°C);[23]

(4-Cl-benzylidene)aniline, 2d: Yield 84%. Time 4 h. mp 64-5°C (lit. mp 63°C);[22]

3-(2-Thenylideneamino)quinoline, 2e : Yield 62%. Time 8 h. mp 82°C (lit. mp 82-4°C).[24]

Reduction of imines. To a warm solution or suspension of the imine (10 mmol) in methanol (10 ml), sodium borohydride (20 mmol) was added in small portions (20 min) and the mixture heated on a steam bath for 2 h with stirring. The reaction mixture was then cooled and treated with water. The product was washed with water and crystallized from ethanol.

4-OCH_3-(*N*-benzyl)aniline: Yield 85%. Time 2 h. mp 64°C (lit. mp 64-64°C);[25]

***N*-(4-OCH_3-benzyl)aniline:** Yield 60%. Time 2 h mp 63-64°C (lit. mp 64.5°C);[21]

4-Cl-(*N*-benzyl)aniline: Yield 83%. Time 2h. mp 43-5°C (lit. mp 46-8°C);[23]

***N*-(4-Cl-benzyl)aniline:** Yield 72%. Time 1.5 h. mp 51-2°C (lit. mp 52-53°C);[23]

3-[(Thiophen-2-ylmethyl)amino]quinoline : Yield 80%.Time 2h. mp 92°C (lit. mp 91-3°C).[24]

EPR experiments. EPR spectra were measured with an EPR Varian E112 instrument. The temperature of the samples was controlled by an Oxford EPR 900 cryostat. The spectrometer was interfaced to a PC Computer 486/100 by means of a data acquisition system, giving on-line signal averaging.[26] The hyperfine coupling constants and linewidths were obtained by computer simulation of the EPR spectra. The spectral optimization software was provided by D. Duling, NIEHS, NIC.[13] The concentration of radicals was determined by comparison with the Varian Strong Pitch, and was obtained by comparison with a standard. In the case of reaction 7, it has been evaluated 4.8×10^{-5} M, that is 0.015% of the initial Schiff base. The g_{iso} values were : Figure 1, spectrum *a* and *c*: 2.0053, spectrum *b*: 2.0055; Figure 4, 2.0032.

NMR experiments. ^1H NMR spectra were recorded on a Bruker AMX300 WB instrument endowed with a variable temperature unit. General procedure: A spectrum of the starting imine, **2a-d**, and **12**, was recorded. After addition of an appropriate volume of concentrated solution of formic, or acetic, or chloroacetic acid in chloroform-*d* with a microsyringe, at room temperature, spectra were registered every 30 minutes for 3 hours; the mixture was then heated inside the probe up to 318 K, and spectra recorded every hour until no further product formation was observed.

In figure 3 we report the spectra for the reaction of **2a** with formic acid. A similar trend was observed in all the examined cases. δ_H ($CDCl_3$) **2a**: 3.85 (3H, s, OCH_3), 6.93-6.96 (2H, d of AA'BB' system, aniline), 7.24-7.27 (2H, d of AA'BB' system, aniline), 7.47 (3H, m, *o,p*-hydrogens, benzylidene), 7.9 (2H, m, *m*-hydrogens, benzylidene), 8.49 (1H, s, benzylic proton); **2a + HCOOH**, room temperature: 3.81 (3H, broad), 6.96 (broad), 7.4 (broad), 7.55 (m,b), 7.97 (d, b), 8.14 (s, HCOOH), 8.63 (s, b), 10.5 (1H, s, HCOOH); **2a + formic acid + heating:** this spectrum shows narrower lines with respect to the former, with additional peaks due to product formation, the most diagnostic signal of which being a singlet at 4.42 ppm, due to the benzylic protons of the amine adduct from imine **2a**.

The reaction of **2d** with HCOOH has been repeated in the presence of isoamylnitrite (5-fold excess with respect to the imine) as free-radical scavenger. Isoamylnitrite, δ_H ($CDCl_3$) : 4.72 (2H, t, -O-CH_2), 1.64 (m, 3H, -CH_2-CH), 0.96-0.93 (6H, d, $(CH_3)_2$); Isoamylnitrite after the spin trap, 3.72 (2H, t, -O-CH_2), 1.70 (1H, m, CH) 0.92-0.89 (6H, d,. $(CH_3)_2$); dimer of isoamyl nitrite radical, signals at 4.2, 1.5, and 0.88 ppm. No signal

attributable to the product (4.3-4.4 ppm) could be detected, even after warming the reaction mixture at 418 K for three hours.

ACKNOWLEDGEMENTS

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