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# POLAR EFFECTS IN FREE-RADICAL REACTIONS. NEW SYNTHETIC DEVELOPMENTS IN THE FUNCTIONALIZATION OF HETEROAROMATIC BASES BY NUCLEOPHILIC RADICALS

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Abstract - The synthetic interest of the direct substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is furtheron developed by the following new achievements: i) utilization of the redox system $\overset{+}{N}H_3OH/Ti(III)$ in several solvents; ii) utilization of benzoyl peroxide in alcohols; iii) carbamoylation by $HCONH_2$ and $H_2O_2$ in the presence of catalytic amounts of Fe(II). These systems allow to obtain either substitution till now tried without success or reactions of industrial interest.Polar effects play a dominat role in determining reactivity, selectivity and synthetic applications; in particular the role of the strongly nucleophilic intermediate radicals of pyridinyl type in the rearomatization step is emphasized.

## INTRODUCTION

We have developed in the last 15 years variety of homolytic substitutions of heteroaromatic bases, leading to C-C bond formation, which on the whole reproduce the Friedel-Crafts reaction, but with opposite reactivity and selectivity owing to the nucleophilic character of the reacting radicals[1]. Also these reactions can be divided in a generalized sense into alkylation and acylation, which include reactions of considerable diversity.

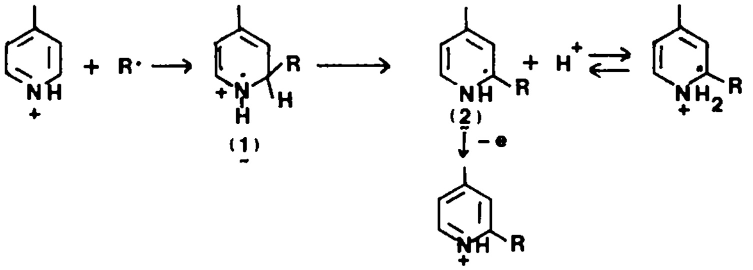
The parallelism between these homolytic substitutions and the classical Friedel-Crafts reaction is related to the fact that generally the more stable the carbonium ion is the more nucleophilic will be the corresponding radical[2]. Thus in principle all the electrophilic species useful in the Friedel-Crafts reaction can be utilized, as corresponding radicals, for the selective substitution of the heteroaromatic bases. Practically all the carbon-centered radicals are suitable, with the exception mentioned for the electrophilic process; that is only radicals with electron-withdrawing groups directly bonded or conjugated to the radical center are not suitable for the homolytic substitution because the decresed nucleophilic character inhibits the reaction.

The great synthetic interest of the heteroaromatic substitution results from three main factors:

i) a very large variety of selective radical sources allow to generate nucleophilic radicals corresponding to most of the electrophilic species utilized in the Friedel-Crafts reaction. Several of the most important classes of organic compounds[1,3] (alkanes, alkenes, alkylbenzenes, alkyl halides, alcohols, ethers, aldehydes, ketones, carboxylic acids, amines, amides, oxaziridines, N-chloramines etc.) can be utilized as radical sources for the homolytic substitution.

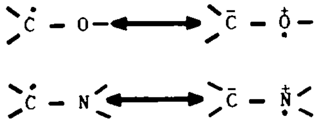
ii) The reactivity (rate constants in the range of $10^5$-$10^8$ $M^{-1}s^{-1}$)[4] and the positional and substrate selectivity in the addition of alkyl and acyl radicals to be protonated heterocyclic ring are exceptionally high and are mainly due to polar effects[1,2].

iii) The rearomatization of the radical adduct (1) is very selective and quite easy and, according to our recent interpretation[3a,b,5] it is due to strongly nucleophilic radicals of the pyridinyl type (2).

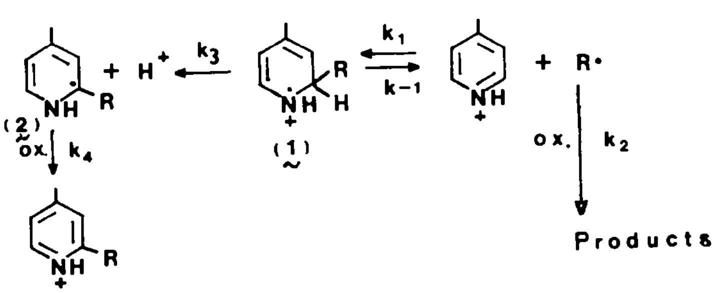


All the other conditions being equal, the reactivity and the selectivity of the reaction increase by increasing the nucleophilic character of the radical[6]. However a too marked nucleophilic character can determine synthetic limitations, due to two factors:

a) The increased nucleophilic character is generally associated with an increased stability and oxidability of the radical; in particular oxygen and nitrogen atoms in α position (i.e., radicals from alcohols, ethers, amines, N-alkylamides) increase the nucleophilicity, the stability and the oxidability of the alkyl radicals[7].

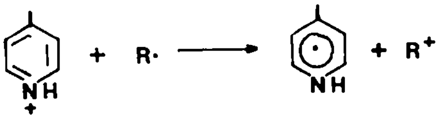


The increased stability can be reflected in the reversibility[4] of the addition of the radical to the heterocyclic nucleus.



Oxidations of the radical adduct 2 and of the nucleophilic radical R· are in general irreversible and the equilibrium is strictly governed by the relative values of the rate constants $k_1$, $k_{-1}$, $k_2$, $k_3$ and $k_4$. On the other hand an oxidizing medium is required for the selective rearomatization of the radical adduct.

b) A too nucleophilic character of the radical can determine favourable redox conditions for an electron-transfer process particularly with bases of high electron affinity, thus preventing the reaction from substitution.



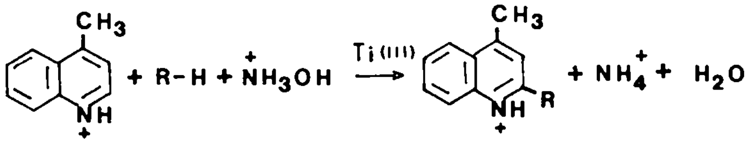
Thus, for example, the hydroxymethylation of heteroaromatic bases with methanol gave good results with a veriety of oxidants, whereas with ethanol only traces of α-hydroxyethylation were obtained under the same conditions and no substitution product was observed with isopropanol[8].

In this paper we report some new synthetic developments, which partly overcome the limitations due to the factor a) by influencing mainly the rate constants $k_2$ and $k_4$. The basic idea arose from the awareness that a strongly nucleophilic pyridinyl radical type is intermediate of the heteroaromatic substitution[3a,b,5] and that therefore a very mild oxidizing medium can be sufficient for the selective rearomatization of the radical adduct.

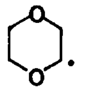
## RESULTS

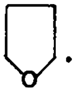
### Substitution with the redox system $\overset{+}{N}H_3OH/Ti(III)$.

When a Ti(III)salt is added to a solution of a hydroxylaminium salt and a protonated heteroaromatic base in several solvents (methanol, ethanol, dioxane, tetrahydrofurane, dimethylformamide) the substitution of the heterocyclic ring with the radicals 3 - 9 arising from the solvent occurs.



R· = $\cdot CH_2OH$, $CH_3\dot{C}HOH$ ,





3 4 5 6

$CHON(CH_3)CH_2\cdot$ , $\cdot CON(CH_3)_2$

7 8 9

Quantitative data have been determined with lepidine (Table 1), which is activated only the position 2, but it has been qualitatively verified that the reaction has a general character for the heteroaromatic bases. Several other solvents can be used, particularly if partly soluble in water, but problems of selectivity in hydrogen abstractions can limit the synthetic applications (see the n-butanol case below).

Table 1: Homolytic substitution at position 2 of protonated lepidine by radicals generated by $\overset{+}{N}H_3OH$/Ti(III) in the presence of solvents

| Solvent | Lepidine: $\overset{+}{N}H_3OH$ | Conversion % | Radical | Yield[a] % |
|---|---|---|---|---|
| MeOH | 1 : 1 | 74 | 3 | 87 |
| MeOH | 1 : 2 | 95 | 3 | 82 |
| EtOH | 1 : 1 | 50 | 4 | 86 |
| EtOH | 1 : 3 | 91 | 4 | 70 |
| Dioxane | 1 : 1 | 66 | 5 | 85 |
| Dioxane | 1 : 2 | 97 | 5 | 85 |
| THF | 1 : 1 | 69 | 6 | 65 |
| | | | 7 | 2 |
| DMF | 1 : 1 | 56 | 8 | 60 |
| | | | 9 | 1 |

[a] Yields of isolated products based on converted base.

The experimental conditions are very simple: the violet coloured solution of Ti(III) salt in water is dropped at room temperature to the solution of $\overset{+}{N}H_3OH$ salt and protonated heteroaromatic base in the chosen solvent until the colour remains; the reaction is very fast, practically a titration. The yields of isolated products are generally good. TLC, GLC and HPLC reveal only the presence of the substitution products and of the starting base; there are no traces of other side-products. The yields of Table 1, less than quantitative, based on converted lepidine, are probably due to losses during the separation procedure because of the complexing properties of the titanium salts.

## Hydroxyalkylation by alcohols and benzoyl peroxide

Thermal and photochemical decomposition of benzoyl peroxide in methanol, ethanol and propanol in the presence of protonated lepidine leads to the substitution of the position 2 by the radicals 3,4,10 and 11.

$CH_3 - CH_2 - \underset{\cdot}{C}HOH$ 10

$CH_3 - \underset{\cdot}{C}H - CH_2OH$ 11

The photochemical process gives as competitive reaction the alkylation of the base, whereas the thermal reaction gives some ketone, coresponding to the oxidation of the secondary alcohol and some olefin by dehydration of the alcohol. The results are summarized in Table 2. With isopropanol no hydroxyalkylation takes place. Also these reactions have a general character for the heteroaromatic bases and other solvents can be used as radical sources (the selectivity of hydrogen abstraction from the solvent by PhCOO· and Ph· radicals determines the nature of the reaction products). The use of alcohols in this work had the purpose to investigate the behaviour of strongly nucleophilic α-hydroxyalkyl radicals.

Table 2: Substitution at position 2 of lepidine by radicals from alcohols and benzoyl peroxide

| Alcohol | Lepidine: $(PhCOO)_2$ | Method | Radical | Conversion % | Yields[a] % | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Alcohol | Ketone | Alkyl | Olefin **17** |
| MeOH | 1 : 1 | Thermal (65°C) | **3** | 76 | 98 | - | - | - |
| MeOH | 1 : 2 | " | **3** | 98 | 95 | - | - | - |
| EtOH | 1 : 1 | Thermal (60°C) | **4** | 24 | 90 | - | - | - |
| EtOH | 1 : 2 | Thermal (79°C) | **4** | 38 | 87 | 13 | - | - |
| EtOH | 1 : 1 | hν | **4** | 23 | 50 | - | 50 | - |
| EtOH | 1 : 2 | hν | **4** | 50 | 89 | 5 | 3 | - |
| EtOH | 1 : 3 | hν | **4** | 68 | 95 | 5 | - | - |
| n-PrOH | 1 : 1 | Thermal (98°C) | **10** | 28 | 41 | 6 | - | - |
| | | | **11** | | 34 | | | 19 |
| n-PrOH | 1 : 2 | " | **10** | 53 | 39 | 13 | - | - |
| | | | **11** | | 20 | - | - | 28 |
| n-PrOH | 1 : 2 | hν | **10** | 62 | 91 | 9 | - | - |

[a] Yields based on converted lepidine.

## Substitution of lepidine by radicals obtained from n-butanol

The following radical sources have been utilized to generate the radicals **12**-**15** by hydrogen abstraction from n-butanol: $\overset{+}{N}H_3OH/Ti(III)$, $\overset{+}{N}H_3OSO_3/Fe(II)$, $\overset{+}{N}H_3OSO_3/Ti(III)$, $H_2O_2/Fe(II)$, $H_2O_2/Ti(III)$, t-BuOOH/Fe(II), t-BuOOH/Ti(III), $S_2O_8^{2-}/Fe(II)$, $S_2O_8^{2-}/Ti(III)$, $S_2O_8^{2-}$, $(PhCOO)_2$.

$CH_3 - CH_2 - CH_2 - \underset{\bullet}{C}HOH$ **12**

$CH_3 - CH_2 - \underset{\bullet}{C}H - CH_2OH$ **13**

$CH_3 - \underset{\bullet}{C}H - CH_2 - CH_2OH$ **14**

$\bullet CH_2 - CH_2 - CH_2 - CH_2OH$ **15**

All the radicals are trapped by lepidine; the results are summarized in Table 3.

## Carbamoylation by $HCONH_2$ and $H_2O_2$

The reaction of protonated heteroaromatic bases with hydrogen peroxide and catalytic amount of Fe(II) salt (0.1-5 %) in formamide at 60-80°C gives good yields of selective carbamoylation of the heterocyclic ring. Some results are summarized in Table 4.

Table 3: Hydroxyalkylation at position 2 of lepidine by the radicals **12**-**15**[a]

| Radical source | Radical attack % | | | |
|---|---|---|---|---|
| | **12** | **13** | **14** | **15** |
| $\overset{+}{N}H_3OH/Ti(III)$ | 43.3 | 11.5 | 41.8 | 3.4 |
| $\overset{+}{N}H_3OSO_3^-/Ti(III)$ | 44.6 | 11.3 | 40.6 | 3.4 |
| $\overset{+}{N}H_3OSO_3^-/Fe(II)$ | 13.1 | 24.1 | 59.1 | 3.7 |
| $H_2O_2/Ti(III)$ | 41.7 | 14.5 | 36.4 | 7.4 |
| $H_2O_2/Fe(II)$ | 2.2 | 31.9 | 51.6 | 14.7 |
| t-BuOOH/Ti(III) | 44.3 | 10.2 | 41.3 | 4.2 |
| t-BuOOH/Fe(II) | 5.7 | 17.3 | 70.2 | 6.8 |
| $S_2O_8^{2-}/Ti(III)$ | 27.7 | 18.5 | 50.6 | 3.2 |
| $S_2O_8^{2-}/Fe(II)$ | 2.7 | 25.4 | 68.6 | 3.3 |
| $S_2O_8^{2-}$ | 6.5 | 24.2 | 65.3 | 4.0 |
| $(PhCOO)_2$ | 59.4 | 12.2 | 28.4 | - |

[a] Redox reactions at 20°C; thermal decomposition of $S_2O_8^{2-}$ and $(PhCOO)_2$ at 80°C.

Table 4: Carbamoylation of heteroaromatic bases by $H_2O_2$ or t-BuOOH and $HCONH_2$

| Heteroaromatic base (10 mmol) | $H_2O_2$ (mmol) | $FeSO_4$ (mmol) | T(°C) | Position of attack | Conversion % | Yield[a] % |
|---|---|---|---|---|---|---|
| Lepidine | 14 | 0.3 | 75 | 2 | 82 | 99 |
| " | (t-BuOOH) 13 | 0.1 | 60 | 2 | 67 | 93 |
| Quinoline | 25 | 0.3 | 60 | 2,4-disubstituted | 100 | 97 |
| Quinaldine | 20 | 0.3 | 60 | 4 | 13 | 100 |
| Isoquinoline | 20 | 0.1 | 60 | 1 | 100 | 100 |
| Quinoxaline | 12 | 0.1 | 60 | 2 | 65 | 88 |
| Acridine | 12 | 0.3 | 80 | 9 | 68 | 82 |
| Pyrazine | 20 | 0.3 | 60 | 2 | 58 | 96 |
| Benzothiazole | 20 | 0.3 | 60 | 2 | 40 | 68 |

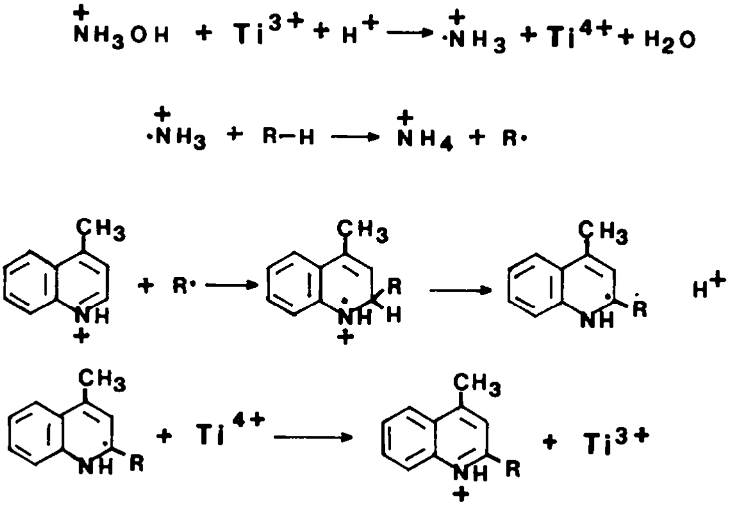
[a] Yields based on converted base.

## DISCUSSION

The substitution reactions reported in this paper concern, with the exception of the phenyl radical, the generation of an electrophilic radical (oxygen- or nitrogen-centered), which does not attack the protonated heteroaromatic base, but abstracts hydrogen atoms from the solvents giving nucleophilic carbon-centered radicals useful for the heteroaromatic substitution.

Hydroxylamine and Ti(III) salt - The awareness that a very mild oxidant can selectively rearomatize the strongly nucleophilic radicals of pyridinyl type, intermediates in the substitution of the heteroaromatic bases, has suggested the possibility to use mild oxidizing redox sources of radicals for such reactions. In particular we have thought that Ti(IV) salt could be an enough oxidizing species to oxidize radicals like 2 and therefore that the well-known[9,10] sources of amino radical, $\overset{+}{N}H_3OH$/Ti(III), could be used in a redox chain for the substitution of protonated heteroatomatic bases by a variety of nucleophilic solvents. Moreover the low oxidizing character of this redox system could allow the utilization of strongly nucleophilic radicals, such as $CH_3\dot{C}HOH$, which previously[8] failed to give significant results with a variety of radical sources.

The results of Table 1 show that, actually, this redox system has the above-mentioned characteristics. The mechanism of this new reaction is shown by the redox chain of Scheme 1.



Scheme 1

The catalyticity, however, is not high because the amino radical is in part reduced by the Ti(III) salt.

$$\cdot\overset{+}{N}H_3 + Ti^{3+} + H^{+} \longrightarrow \overset{+}{N}H_4 + Ti^{4+}$$

The reaction has, for the first time, allowed to obtain satisfactory results with the α-hydroxyalkyl radicals from primary alcohols. Previous attempts[8] have utilized $H_2O_2$, t-BuOOH, $S_2O_8^{2-}$, $\overset{+}{N}H_3OSO_3^-$ in redox (with Fe(II) ) and thermal decomposition. All these radicals sources had given variable results with methanol, but only traces of substitution products with enthanol under the same conditions. On the other hand with all the intermediate radicals ethanol is a more efficient source of α-hydroxyalkyl radical than methanol and the very poor attack with ethanol must be, therefore, related to the higher reversibility of the radical attack and to the faster competitive, irreversible oxidation of the α-hydroxyalkyl radical 4 compared with radical 3.

$$CH_3\dot{C}HOH + Fe^{3+} \longrightarrow CH_3CHO + Fe^{2+} + H^+$$

$$CH_3\dot{C}HOH + S_2O_8^{2-} \longrightarrow CH_3CHO + HSO_4^- + SO_4^{\dot{-}}$$

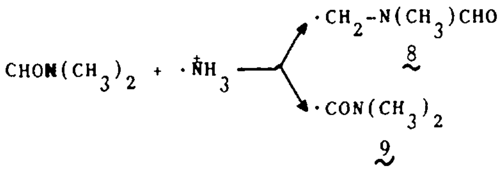
$$CH_3\dot{C}HOH + \overset{+}{N}H_3OSO_3^- \longrightarrow CH_3CHO + HSO_4^- + \cdot\overset{+}{N}H_3$$

Hydroxylamine and Ti(IV) salt are much less oxidizing species and good results are obtained also with ethanol. However, under identical reaction conditions, the conversions of lepidine are somewhat higher with methanol than with ethanol; that means that also Ti(IV) salt oxidizes, to some extent, the α-hydroxyethyl radical.

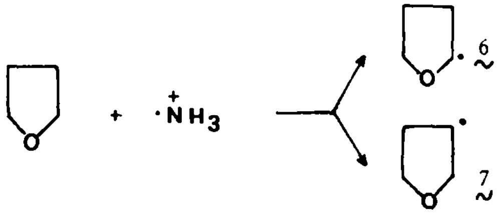
$$CH_3\dot{C}HOH + Ti^{4+} \longrightarrow CH_3CHO + Ti^{3+} + H^+$$

With isopropanol no substitution product with the $CH_3\dot{C}(OH)CH_3$ radical was observed. Either the increased reversibility or the electron-transfer process can explain the failure with isopropanol. We are inclined to consider more probable the electron-transfer process on the ground of the following facts: i) the redox potentials (-0.98, -1.18 and -1.30V for $\cdot CH_2OH$, $CH_3\dot{C}HOH$ and $CH_3\dot{C}(OH)CH_3$ respectively[11]); ii) no trace of substitution product was observed with all the used radical sources; iii) the rates of electron-transfer process are very high (close to the diffusion control limit) when they are exoergonic[12]; iv) polar effect are more important than steric effects in determining the reactivity of the alkyl radical towards the heteroaromatic ring (t-Bu radical is more reactive than n-Bu radical[4]).

With tetrahydrofuran and dimethylformamide the hydrogen abstraction occurs at both types of C-H bonds.



$$CHON(CH_3)_2 + \cdot\overset{+}{N}H_3 \longrightarrow \begin{cases} \cdot CH_2-N(CH_3)CHO & \mathbf{8} \\ \cdot CON(CH_3)_2 & \mathbf{9} \end{cases}$$



Both the solvents have been previously[1,3c,8b] utilized by us in heteroaromatic substitutions with different radical sources and the ratios **6**:**7**, **8**:**9** obviously depend on the nature of the abstracting radical. However these reactions are also strongly affected by the oxidizing medium; thus the results of Table 5 show that when the radical $\cdot\overset{+}{N}H_3$ is generated by the redox source $\overset{+}{N}H_3OSO_3^-/Fe(II)$ the ratios of products obtained from 6-7 and 8-9 are strongly depending on the amount of Fe(III) salt. Whereas they are independent on the amount of Ti(IV) salt with the redox source $\overset{+}{N}H_3$/Ti(III).

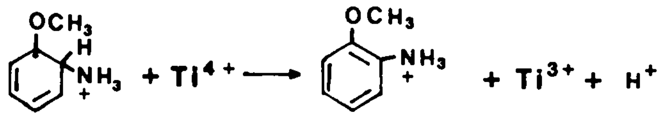
$$\overset{+}{N}H_3OSO_3^- + Fe^{2+} \longrightarrow \cdot\overset{+}{N}H_3 + SO_4^{2-} + Fe^{3+}$$

Table 5: Substitution at the position 2 of protonated lepidine by the radicals 6,7,8,9 obtained from $\cdot\overset{+}{N}H_3$, THF and DMF

| Radical source | Metal salt ( mol %) | Solvent | 2-Substituted lepidine | |
|---|---|---|---|---|
| | | | 6 : 7 | 8 : 9 |
| $\overset{+}{N}H_3OSO_3^-$/Fe(II) | - | THF | 18 | - |
| " | Fe(III) (3) | " | 12 | - |
| " | Fe(III) (7) | " | 6 | - |
| " | Fe(III) (15) | " | 2.5 | - |
| $\overset{+}{N}H_3OH$/Ti(III) | - | " | 32 | - |
| " | Ti(IV) (30) | " | 31 | - |
| $\overset{+}{N}H_3OSO_3^-$/Fe(II) | - | DMF | - | 13.3 |
| " | Fe(III) (1) | " | - | 5.2 |
| " | Fe(III) (3) | " | - | 2.3 |
| " | Fe(III) (5) | " | - | 1.8 |
| " | Fe(III) (7) | " | - | 1.4 |
| " | Fe(III) (13) | " | - | 0.7 |
| $\overset{+}{N}H_3OH$/Ti(III) | - | " | - | 60 |
| " | Ti(IV) (30) | " | - | 57 |

We have recently [3c,5,8b] discussed the cause of the results with $\overset{+}{N}H_3OSO_3^-$ : Radical 6 is much more nucleophilic and oxidable than radical 7 for the proximity of oxygen atom and the radical 8 is more oxidable than the radical 9 because the former is a π and the latter is a σ radical. Thus the radicals 6 and 8 are oxidized very fast by the Fe(III) salt, but not by the Ti(IV) salt and the overall selectivity of the heteroaromatic substitution is quite different with the two different radical sources, although the intermediate abstracting radical is identical.

The results with $\overset{+}{N}H_3OH$/Ti(III) in this work parallel the behavior of the homolyclic aromatic compounds with the radical $\cdot\overset{+}{N}H_3$ from the same source: With benzene the addition of the amino radical to the aromatic ring is not followed by the rearomatization because Ti(IV) salt is not able to oxidize the aminocyclohexadienyl radical adduct[10]. With anisole, however, which gives rise to the more oxidable α-oxydienyl radical 16, structurally similar to the α-aminodienyl radical 2, the rearomatization cleanly occurs[10].



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## Benzoyl peroxide and alcohols

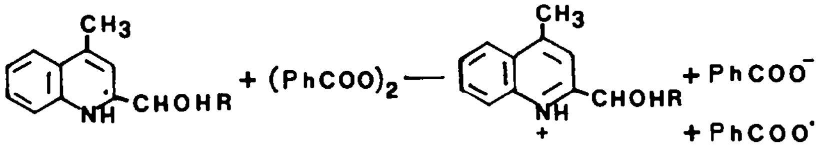
The decomposition rate of benzoyl peroxide in alcoholic solvents is increased by a chain induced decomposition.

$$(PhCOO)_2 \longrightarrow 2\ PhCOO\cdot \longrightarrow 2\ Ph^{\cdot} + 2\ CO_2$$

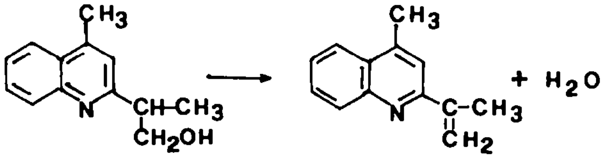
$$PhCOO\cdot(Ph\cdot) + R - CH_2OH \longrightarrow PhCOOH\ (PhH) + R - \dot{C}HOH$$

$$R\text{-}\dot{C}HOH + (PhCOO)_2 \longrightarrow R\text{-}CHO + PhCOOH + PhCOO\cdot$$

In the presence of the protonated base, the attack of the α-hydroxyalkyl radical to the heterocyclic ring competes with its oxidation. The balance between heteroaromatic substitution and oxidation of the secondary α-hydroxyalkyl radical is, however, less favourable with benzoyl peroxide compared with the redox system $\overset{+}{N}H_3HO/Ti(III)$. Much better results are obtained with methanol, whereas with isopropanol no substitution takes place. The fast rearomatization of the pyridinyl radical by induced decomposition of benzoyl peroxide plays an important role in the substitution.



The results obtained in thermal and photochemical decomposition of benzoyl peroxide differ in three main aspects: i) In addition to the hydroxyalkylation some alkylation is obtained in the photochemical process. In the absence of benzoyl peroxide only alkylation occurs; the extent of the alkylation is strictly related to the amount of benzoyl peroxide (Table 2): The increase of the amount of benzoyl peroxide minimized the alkylation reaction. That means that under the used conditions the photochemical decomposition of benzoyl peroxide is faster than the photochemical excitation of the heterocyclic compound, which leads to the alkylation reaction[13]. ii) In the reaction of n-propanol the photochemical process only gives the α-hydroxyalkylation whereas the thermal process gives comparable amounts of α- and β-hydroxyalkylation. A plausible explanation is the fact that the photochemical process takes place at lower temperature and the hydrogen abstraction mainly occurs by PhCOO$^{\bullet}$ radical, which for its electrophilic character is selective in the α position. The higher temperature of the thermal decomposition favours the decarboxylation of the PhCOO$^{\bullet}$ radical with formation of the phenyl radical, which is less selective in hydrogen abstraction. The ratio of α and β-hydroxyalkylation does not, however, reflect the ratio of the hydrogen abstraction because the β-hydroxyalkyl radical is not oxidized by benzoyl peroxide and its addition to the heterocyclic ring is not reversible, contrary to the behaviour of the α-hydroxyalkyl radical. iii) The thermal process with primary alcohols leads to minor amounts of ketones and olefins as byproducts  ketones are formed in smaller amounts in the photochemical process, in which no olefin was observed. The study of the behavior of the formed alcohols has shown that the different temperature is again the cause of these results. It has been, in fact, verified that the β-hydroxyalkylderivatives at the reaction temperature lose water in the thermal process giving the corresponding olefin 17.



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Moreover the α-hydroxyalkylderivatives in the presence of benzoyl peroxide are oxidized to ketones in the thermal process.

## Hydroxyalkylation by n-butanol

All the possible carbon-centered radicals 12-15 are formed by hydrogen abstraction from n-butanol with $\cdot\overset{+}{N}H_3$, ·OH, t-BuO·, $SO_4^{\cdot -}$, Ph·, PhCOO· radicals and are trapped by lepidine in position 2. Several factors contribute to determine the isomer distribution of Table 3: The rates of hydrogen abstraction, addition of the radicals to the heterocyclic ring and oxidation by the radical sources are particularly important. The following features can be evinced from the data of Table 3. i) The α-hydroxyalkylderivative is the prevailing isomer when the reaction medium does not fast oxidize the radical 12. That occurs with benzoyl peroxide and when Ti(III) salt is a component of the redox system. with the exception of $S_2O_8^{2-}$ , which is itself an efficient oxidant of the α-hydroxyalkyl radicals. When Fe(III) salt is present, also at very low concentration, the fast oxidation of 12 reduces the extent of its attack to the heterocyclic ring. ii) The substitution by the radical 14 is always prevailing over the substitution by the radical 13. Polar effects favour this behaviour either in hydrogen abstraction[14] (the abstracting radical is generally electrophilic) or in the heteroaromatic addition[7] (the radical 14 is more nucleophilic then the radical 13). The radical 15 is formed less efficiently for enthalpic reasons[14].

## Carbamoylation by $HCONH_2$ and $H_2O_2$

The carbamoylation of the heteroaromatic bases by the $\cdot CONH_2$ radical has been previously obtained by us from $HCONH_2$ and a variety of oxidants[1a]. Hydrogen peroxide is the cheapest among these oxidants. Thermal and photochemical decomposition gave, however, poor results. The redox decomposition at room temperature gave much better results, but it required almost stoichiometric amounts of Fe(II) salt, which partly is oxidized.

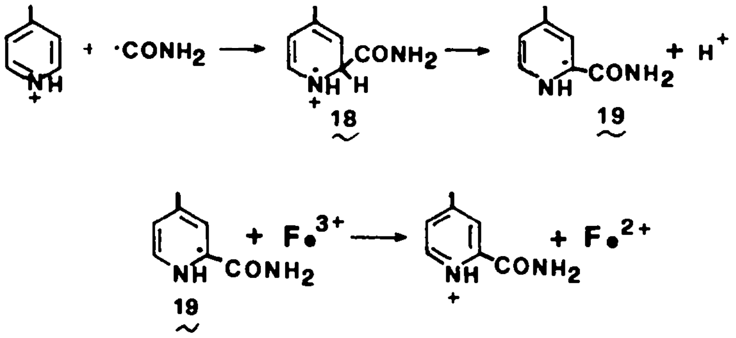
$$H_2O_2 + Fe^{2+} \longrightarrow HO^{\cdot} + Fe^{3+} + OH^-$$

$$HO^{\cdot} + Fe^{2+} \longrightarrow HO^- + Fe^{3+}$$

The awareness that an easily oxidizable radical of pyridinyl type is involved in the rearomatization step suggested us that a small concentration of Fe(III) salt should be sufficient for a clean and selective rearomatization of the heteroaromatic radical adduct. Thus we have developed a new procedure by combining thermal and redox processes, which is very efficient and requires only catalytic amount of iron salt (0.1 - 3%). The mechanism of Scheme 2 explains the results.

$$H_2O_2 + Fe^{2+} \longrightarrow HO\cdot + OH^- + Fe^{3+}$$

$$HO\cdot + HCONH_2 \longrightarrow H_2O + \cdot CONH_2$$



Scheme 2

Radical 19 is formed very easily by loss of a proton from 18 for polar reasons and because it is an allylic captodative[15] radical. In which the stabilizing effects of the substituents are, at least, additive.

At room temperature with the same amount of iron salt only traces of substutution products are formed; without iron salt under the same conditions used in Table 4 no reaction occurs.

Some results, summarized in Table 4, show that this new process, for the experimental simplicity, the cheap reagents, the high yields and selectivity and the practical interest of the reaction products, has all the features for industrial applications[16]. Compared with the redox process at room temperature this new procedure has in fact three main important practical advantages: It utilizes only catalytic amount of $FeSO_4$, gives higher yields based on $H_2O_2$ and allows a much easier separation of the reaction products. The catalytic process can be carried out also by using t-BuOOH instead of $H_2O_2$.

## EXPERIMENTAL

Analytical GLC analyses were performed with a Carlo Erba 4200 or a Dani 3600 instrument equipped with flame ionization detectors. Quantitative TLC analyses were performed by using a CAMAG TLC scanner at 280 nm (Hg lamp) on HPTLC (Merk). In all cases peak areas were determined with a Spectra Physics SP 4100 integrator as mean value of two independent experiments.

**Substitutions with the redox system $\overset{+}{N}H_3OH/Ti(III)$: General procedure** - The heteroaromatic base (4 mmol), $H_2SO_4$ (4 mmol), $NH_2OH \cdot H_2SO_4$ (in the amount reported in Table 1) and the solvent (20 mL) were introduced in a 50 mL flask. The solution was flushed with $N_2$ and a violet coloured solution of $Ti_2(SO_4)_3$ in water (0.7 N) was dropped under stirring at room temperature until the colour remains. The reaction is very fast, practically a titration. The solution was then diluted with water (3 g of sodium citrate was added), basified with $NH_3$ and extracted with $CH_2Cl_2$. All the reaction products were isolated by silica gel chromatography and identified by comparison (IR, NMR, MS) with authentic samples, previously obtained by us with different procedures[3c,8,17]. The results are reported in Tables 1,3 and 5.

**Substitutions by the redox system $\overset{+}{N}H_3OSO_3^-/Ti(III)$, $H_2O_2/Ti(II)$, t-BuOOH/Ti(III), $S_2O_8^{2-}/Ti(III)$:** A procedure similar to the one reported for $NH_3OH$ was used. The results are reported in Table 3. The isomers obtained from n-butanol and lepidine were identified by combined GLC-MS.

**Isomer from 12:** MS: m/e (rel.int.) : 214(0.52), 198(7.66), 186(11.48), 173(100), 172(67.24), 170(8.40), 157(4.13), 143(15.82), 142(15.04).

**Isomer from 13:** MS : m/e (rel.int.) : 214(1.89), 1.98(31.84), 186(71.89),184(61.76), 170(100), 157(23.52), 143(10.99), 142(5.07).

**Isomer from 14:** MS : m/e (rel.int.) : 214(1.27), 198(6.44), 194(12.49), 184(29.39), 171(100), 157(4.49), 143(11.25), 142(4.69).

**Isomer from 15:** MS : m/e (rel.int.) : 214(5.82), 198(24.15), 194(12.01), 184(28.82), 170(78.26), 157(100), 143(12.39), 142(6.95).

The NMR spectrum of the mixture of the isomers does not reveal signals at $\delta > 8.2$ showing that the position 2 of lepidine is substituted.
Quantitative GLC analyses were performed by using a capillary column OV1.

**Substitutions by the redox systems $\overset{+}{N}H_3OSO_3^-/Fe(II)$, $H_2O_2/Fe(II)$, t-BuOOH/Fe(II) and $S_2O_8^{2-}/Fe(II)$:** The procedure, previously developed by us[3c,8], have been utilized. The results are reported in Tables 3 and 5.

**Substitution by the thermal decomposition of $S_2O_8^{2-}$ :** The procedure, previously developed by us[8a], has been utilized. The result obtained with n-butanol is reported in Table 3.

**Substitution with benzoyl peride and alcohols: General procedure** - a) In a 50 mL flask, equipped with magnetic stirrer and reflux condenser, were introduced 25 mL of alcohol, 2 mmol of lepidine, 2 mmol of $CF_3COOH$ and benzoyl peroxide in the amounts reported in Table 2. The solution was flushed with $N_2$ and warmed at the temperatures reported in Table 2 until complete decomposition of benzoyl peroxide. The solution was then diluted with water, made basic with 10% NaOH solution and extracted with $CH_2Cl_2$. The reaction products were isolated by silica gel chromatography and identified by comparison (IR, NMR, MS) with authentic samples previously obtained by us[8]. The olefin 17 has been characterized by NMR and MS: H-NMR($CDCl_3$): 7.3-8.2 (m, 5H), 5.6(d, 2H), 2.6(s, 3H), 2.3(s, 3H). MS : m/e : 183($M^+$), 168, 157, 143, 115.

Quantitative analyses have been performed by GLC and HPTLC plates by using calibration curves for starting and final products obtained from five solutions of the same volume and containing different amounts of products. The results are reported in the Tables 2 and 3. b) Photochemical process - A solution of 1 mmole of lepidine, 1 mmol of $CF_3COOH$ and benzoyl peroxide (in the amount reported in Table 2) in 25 mL of alcohol in a quartz vessel was irradiated at room temperature under nitrogen at 300 nm in a RPR-100 Rayonet photochemical reactor for 2 h. The same procedure of a) was then utilized for the isolation and the analysis of the reaction products.

$H_2O_2$ or t-BuOOH and $FeSO_4.7H_2O$ in the amounts reported in Table 4 were added to a solution of 10 mmol of the heteroaromatic compound, 10 mmol of $H_2SO_4$ in 100 mL of formamide. The solution was warmed for 4 h at the temperatures reported in Table 4. The solution was then diluted with water, made basic with 10% NaOH and extracted with $CH_2Cl_2$. The reaction products, isolated by silica gel chromatography, were identified by comparison (IR, NMR, MS) with authentic samples[18]. The quantitative analyses were performed by GCL. The results are reported in Table 4.

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