RECENT DEVELOPMENTS OF FREE-RADICAL SUBSTITUTIONS OF HETEROAROMATIC BASES

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Abstract - The most recent mechanistic and synthetic aspects of the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals are reviewed. From mechanistic point of view the following aspects are discussed; i) Structure-reactivity relationship; ii) Rearomatization of the radical adducts; iii) Solvent and isotope effects; iv) Overlap area with ionic reactions.
The synthetic developments concern the following topics: i) Selectivity with carbonyl radicals; ii) Alkyl iodides as sources of alkyl radicals; iii) Alkylation by carboxylic acids; iv) Vinylation by olefins; v) Oxyalkylation by ethers; vi) Catalytic processes; vii) Substitution with strongly nucleophilic radicals.

Free-radical reactions were considered for long time synonymous with unselectivity. Apart from the uninterrupted theoretical interest and the importance in the basic chemical industry (vinyl polymerization, oxidation by molecular oxygen, chlorination of methane etc., in which the use of structurally simple molecules makes less dramatic the problems of selectivity), they were considered of poor interest by the organic chemists, with few exceptions, for the synthesis of fine chemicals and complex molecules, where a high selectivity is an essential condition for the synthetic success.
Barton has been the most important among these exceptions: ever since 1960 he has been a precursor showing by the "Barton reaction"[1] the synthetic potentiality of the free-radical reactions for the selective synthesis of complex molecules.
In the last 15 years free-radical reactions have, however, gained a remarkable position among the selective methods of synthesis of sophisticated molecules and have been noticed as the important factor in biological processes[2]. In this development the Barton research has played a leadership and a drawing role.
In 1968 we have showed, in a preliminary report[3], that a variety of selective reactions could be realized by taking advantage of the polar effects arising from the nucleophilic character of the carbon-centered radicals in the reactions with

electron-deficient substrates (olefins conjugated with electron-withdrawing groups, protonated heteroaromatic bases, quinones, biacetyl). Electron-poor olefins and heteroaromatic bases were revealed to be particularly interesting for the syntheticinvolvements; the alkylation of these olefins has shown a large synthetic potentiality[4], and the substitution of heteroaromatic bases by nucleophilic carbon-centered radicals has been developped as one of the most important general reactions in heteroaromatic series[5]. The great interest of this last reaction results from the fact that it reproduces most of the numerous aspects of the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity. The most recent mechanistic and synthetic involvements, to which also Barton[6] has brought a relevant contribution, will be reviewed in this paper.

MECHANISM OF THE SUBSTITUTION OF PROTONATED HETEROAROMATIC BASES WITH NUCLEOPHILIC CARBON-CENTERED RADICALS

As for all the homolytic aromatic substitutions, the overall process is characterized by three steps:

i) Generation of the carbon-centered radical (eq. 1)

$$\text{Source} \longrightarrow \text{R}\cdot \qquad (1)$$

ii) Addition to the protonated heterocyclic ring (eq. 2)

$$\left[\text{Het-H}\right]^{+} + \text{R}\cdot \longrightarrow \left[\text{Het}\begin{smallmatrix}\text{H}\\ \text{R}\end{smallmatrix}\right]^{+\cdot} \qquad (2)$$

iii) Rearomatization of the radical adduct (eq. 3)

$$\left[\text{Het}\begin{smallmatrix}\text{R}\\ \text{H}\end{smallmatrix}\right]^{+\cdot} \longrightarrow \left[\text{Het-R}\right]^{+} \qquad (3)$$

Carbon-centered radicals are reactive species and react fast in a large variety of interactions (hydrogen and halogen abstraction, addition to unsaturated systems, oxidation, reduction, isomerization, dimerization, disproportionation, etc.). Particularly they react with most of the common solvents utilized in organic synthesis. Thus a high regio- and chemoselectivity are required as prelimilary condition for the synthetic success.

a) Structure-reactivity relationship in the reaction of carbon-centered radicals with protonated heteroaromatic bases

Table 1 shows some rate constants for the addition of carbon-centered radicals to benzene, protonated and unprotonated heteroaromatic bases. These and hundreds of similar results[5] indicate that a highly regioselective addition occurs with protonated heteroaromatic bases.

TABLE 1 - Rate constant ($M^{-1}s^{-1}$) for the addition of carbon-centered radicals to benzene and heteroaromatic bases (protonated)

Aromatic substrate	Radical				
	n-Bu [7]	t-Bu [8]	$.CH_2OH$ [9]	t-BuĊO [10]	Ph. [11]
Benzene	3.8×10^{2}	no reaction	no reaction	no reaction	1.03×10^{6}
4-Methylpyridine [a]	1.3×10^{3}	"	"	"	3.2×10^{5}
4-Methylpyridine	1.1×10^{5}	-	-	-	1.8×10^{6}
4-Acetylpyridine	6.8×10^{5}	4.6×10^{6}	-	-	-
4-Cyanopyridine	1.8×10^{6}	6.7×10^{6}	$>10^{7}$	$>10^{6}$	6.1×10^{6}
Quinoline	8.5×10^{5}	4.1×10^{6}	$>10^{7}$	$>10^{6}$	-
Lepidine	5.7×10^{5}	-	-	-	-
Quinoxaline	2.8×10^{7}	-	-	$>3.10^{6}$	-
Benzothiazole	9.9×10^{5}	-	-	$>7.10^{5}$	-

a) Unprotonated 4-methylpyridine

All the carbonyl radicals and the alkyl radicals without electron-withdrawing groups in the α position exclusively attack the position of the protonated heterocyclic ring of high nucleophilic reactivity (α and γ), whereas with the aryl radicals, less nucleophilic than alkyl and carbonyl radicals, the regioselectivity is lower (generally all the free aromatic positions are attacked to some extent). Alkyl radicals with electron-withdrawing substituents (COOR, COR, NO_2, CN, SO_2R etc.) in the α position do not react with protonated heteroaromatic bases.

The results of Table 1 emphasize some fundamental aspects of the reaction:

i) The unprotonated bases are generally as reactive and selective as benzene derivatives (all the free aromatic positions are attacked). The protonation causes a high increase of reactivity and selectivity for alkyl and carbonyl radicals, but does only a moderate increase for the phenyl (and in general aryl) radical.

ii) The rates of addition of alkyl and acyl radicals to protonated heteroaromatic bases are much higher than those of most of the possible competitive reactions of the same radicals, particularly with the common solvents. That makes successful the use of a large variety of radical sources and carbon-centered radicals.

iii) t-Alkyl, hydroxymethyl and acyl radicals are more reactive than primary alkyl radicals, in spite of the fact that the addition enthalpy is unfavourable and also the steric effect is unfavourable with t-alkyl radicals. The polar effect clearly appears to be the dominant factor in determining the reactivity; such is also the case with their high regioselectivity.

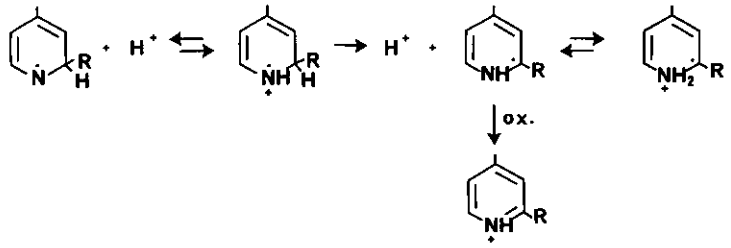
iv) The phenyl is a highly reactive, unselective radical, in agreement with the Reactivity-Selectivity Principle. However, the Principle can be reversed when polar effects are dominant. Thus the phenyl radical is often much more reactive and less selective than the alkyl and acyl radicals; that occurs also in the addition to benzene. However, with protonated heteroaromatic bases acyl and alkyl radicals are not only much more selective, but more reactive than the phenyl radical, once again showing the dominant role of the polar effect. This last affects the rates of the radical additions to the heteroaromatic ring by decreasing the activation energy as the electron-deficiency of the heterocyclic ring increases (Table 2)

TABLE 2 - Arrhenius parameters for the addition of primary alkyl radicals to protonated heteroaromatic bases[7]

Heteroaromatic base	E_a (Kcal/mol)	log A
4-Methylpyridine	6.9	9.2
4-Methylquinoline	5.9	9.2
4-Cyanopyridine	4.9	9.3
Quinoxaline	2.8	9.3

b) Rearomatization of the radical adducts

The mechanism, illustrated by eq. 4, has been envisaged in the rearomatization step of the heteroaromatic substitution[12,13] (eq. 4)



(4)

Clearly this mechanism can work for the attack at the α and γ, but not in other positions of heteroaromatic compounds. That can contribute, in addition to the polar effects, to the high regioselectivity of the substitution, particularly when the radical addition is reversible.

Several direct and indirect evidences support the mechanism of eq. 4.

The enthalpy change for the loss of proton in the trimethyl-amino radical cation (eq. 5) has been estimated[14] at about 6 Kcal/mol.

$$Me_3\overset{+}{N}\cdot \longrightarrow Me_2N\text{-}\dot{C}H_2 + H^+ \rightleftharpoons Me_2\overset{+}{N}H\text{-}\dot{C}H_2 \qquad \Delta H \sim 6 \text{ Kcal/mol} \qquad (5)$$

The enthalpy change for the similar process of eq. 4 must be even more favourable, considering the higher stability of the pyridinyl radical, which is at the same time an α-aminoalkyl and an allyl radical. The loss of the proton from the α-C-H bond of the amino radical cations must be considered irreversible because of the much higher proton affinity of the nitrogen compared to that of the α-carbon.

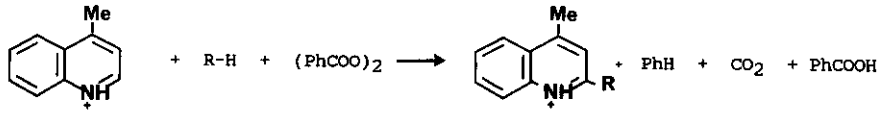
On the other hand pyridinyl radicals are very weakly basic compared to the corresponding dihydropyridines[15] and the unprotonated radical must be present in significant amount at the equilibrium in not strongly acidic medium.

$pK_a \sim 2\text{-}3$ $\qquad$ $pK_a \sim 7$

Moreover, the ionization potential of α -aminoalkyl radicals (5.4-6.1 eV) are the lowest among so far observed organic or organometallic species[16], close to those of lithium (5.39 eV) and sodium (5.14 eV), indicating that the pyridinyl radicals can behave as potent reducing agent towards weak oxidants. That contributes to make fast and selective the rearomatization of the heterocyclic radical adduct (eq. 4).

Kinetic studies[13b] strongly support the mechanism of eq. 4. Several sources of nucleophilic alkyl and carbonyl radicals undergo, in fact, a marked induced decomposition during the heteroaromatic substitution.

Thus, for example, the thermal decomposition of benzoyl peroxide in several solvents (R-H) in the presence of protonated lepidine gives high yields of substitution according to eq. 6.



(6)

R-H = $H-CH_2OH$,  , $CHON(Me)CH_2-H$, $H-CONMe_2$, $C_6H_{11}-H$

At the same time a remarkable induced decomposition of the peroxide (Table 3) is observed and the reaction is inhibited by the presence of oxygen.

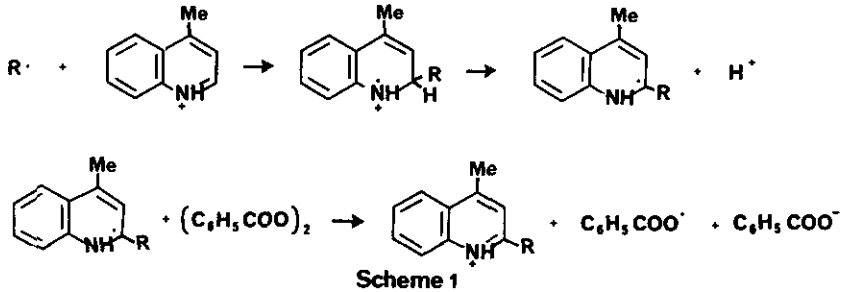
TABLE 3 - Apparent first-order rate constants for the decomposition of benzoyl peroxide[13b]

Solvent	[Lepidine] mol L^{-1}	Benzoyl peroxide mol L^{-1}	T °C	$10^4 k$ s^{-1}
Dioxane	0.084	0.084	60	2.76
"	-	0.084	60	0.62
"	0.042	0.042	80	17.80
"	-	0.042	80	2.76
Methanol	0.042	0.042	60	1.61
"	-	0.042	60	0.19
DMF	0.042	0.042	60	2.45
"	-	0.042	60	0.95
Cyclohexane	0.044	0.022	72	1.06
"	-	0.022	72	0.19

A free-radical chain mechanism (Scheme 1) explains the kinetic behaviour.

$$(PhCOO)_2 \longrightarrow 2\ PhCOO\cdot \longrightarrow 2\ Ph. + CO_2$$

$$R\text{-}H + Ph.(PhCOO.) \longrightarrow R. + PhH(PhCOOH)$$



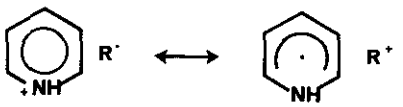
Scheme 1

The high reducing ability of the pyridinyl radical makes fast and selective the one-electron reduction of the benzoyl peroxide, causing a significant induced decomposition and a chain process.

Similar induced decompositions were observed[13b] during the substitution of lepidine with benzoyl peroxide and alkyl iodides, with lauroyl peroxide and with peroxydisulphate and carboxylic acid indicating the general feature of the kinetic behaviour, which supports the mechanism of the rearomatization step.

c) Solvent and isotope effect

Few cases are known where solvents do have significant effects on the rates and selectivity of free-radical reactions. From a general point of view the solvent effect could be significant when polar effects and charged species are involved in free-radical reactions because polar transition states are involved. The results of Table 1 and 2 clearly indicate that the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radical is characterized by large polar effects, and explained by transition states similar to charge-transfer complexes[5] (eq. 7)



(7)

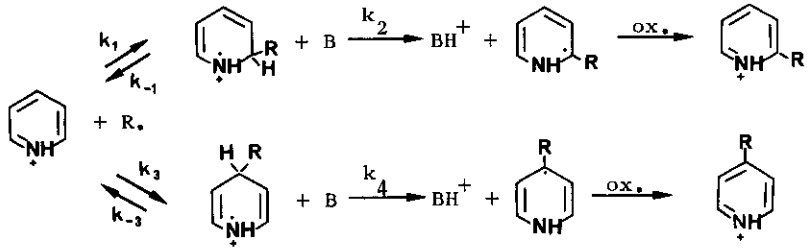
Actually, we have observed[13a] a significant solvent effect, which remarkably affects the regio- and chemoselectivity, and also the deuterium isotope effect in the substitution of protonated pyridines by nucleophilic carbon-centered

radicals, as the results of the Tables 4, 5 and 6 show.

Particularly the results of Table 4 show that only the α and γ positions of protonated pyridine are attacked, with the exception of phenyl radical which attacks also at the β-position in small amount (4-6 %). The regioselectivity is independent of the radical source, but it depends mainly on the solvent. This dependence is small but still significant with the phenyl radical (the least nucleophilic), and it progressively increases with the increase of the nucleophilicity of the radical from methyl to primary, secondary, tertiary alkyl, dioxanyl and α-THF radicals. With the most nucleophilic radicals (t-Bu, α-THF) no substitution was observed with unprotonated pyridine, clearly showing that only the protonated base is involved in the substitution. With the benzyl radical no substitution was observed even with protonated pyridine, but bibenzyl was the only reaction product; with more activated bases, such as cyanopyridines, quinolines, quinoxalines, the benzyl-substituted products were easily obtained[17] (see also Table 6).

The increased isotope effect (Table 5) reflects an increased reversibility of the radical addition, which is related to the reaction enthalpy.

Thus the general mechanism of the reaction is illustrated by the Scheme 2.



Scheme 2

Eqs. 8 and 9 account for the rates of the α and γ positions.

$$k_{\alpha\,obs.} = \frac{k_1 k_2 [B]}{k_{-1} + k_2 [B]} \qquad (8) \qquad\qquad k_{\gamma\,obs.} = \frac{k_3 k_4 [B]}{k_{-3} + k_4 [B]} \qquad (9)$$

k_2 and k_4 are sensitive to the isotopic composition of the substrate, whereas $k_1 (k_{-1})$ and $k_3 (k_{-3})$ are effectively independent of it. Consequently, an increase in the partition factors, $k_{-1}/k_2[B]$ and $k_{-3}/k_4[B]$, moving the

kinetic control towards the second step, increases the sensitivity of the reaction to base catalysis and the magnitude of the kinetic isotope effect.

TABLE 4 - Solvent effect on the regioselectivity in the substitution of protonated pyridine[13a]

Radical	Solvent	α %	γ %
Ph [a]	Water	63.8	31.9
Ph [a]	Benzene	70.2	23.8
Me	Water	62.3	37.7
Me	Benzene	73.2	26.7
n-Bu	Water	56.3	43.7
n-Bu	MeCN	64.5	35.5
n-Bu	Benzene	73.8	26.2
i-Pr	Water	31.7	68.3
i-Pr	Water:MeCN (1:4)	32.0	68.0
i-Pr	$HCONH_2$	43.8	56.2
i-Pr	Me_2SO	46.1	53.9
i-Pr	MeCN	56.3	43.7
i-Pr	MeCONHMe	59.3	40.7
i-Pr	$MeCONMe_2$	61.3	38.7
i-Pr	Benzene	72.8	27.2
t-Bu	Water	23.0	77.0
t-Bu	Benzene	71.4	28.6
Dioxanyl	Dioxane:H_2O (1:1)	25.5	74.5
Dioxanyl	Dioxane	76.3	23.4
α-THF	THF:H_2O (1:1)	20.0	80.0
α-THF	THF	85.8	14.2
Benzyl [b]		no reaction	

a) Small amounts (4-6 %) of the β isomer were formed.

b) Bibenzyl is the main reaction product.

TABLE 5 - Deuterium isotope effect in the substitution of protonated pyridine[13a]

Radical	Solvent	α	k_H/k_D
Ph	Water	1.0	1.0
Ph	Benzene	1.0	1.0
i-Pr	Water	3.9	4.2
i-Pr	Benzene	1.7	1.9
α-THF	THF:H_2O (1:1)	7.7	6.6
α-THF	THF	2.5	2.3
α-THF	THF:MeCN (1:1)	4.5	3.5

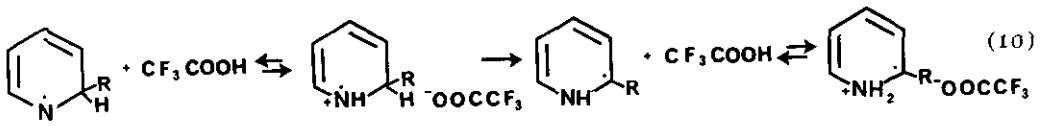
With phenyl radical, no isotope effect has been observed, indicating that the first step of the mechanism of the Scheme 2 is rate-determining : $k_{-1} \ll k_2[B]$ and $k_{-3} \ll k_4[B]$, the terms in $[B]$ fall out; $k_{obs} = k_1$ or k_3 and the addition to the pyridine ring is substantially irreversible.

The behaviour of the benzyl radical must be ascribed to the other extreme, when $k_{-1} \gg k_2[B]$ and $k_{-3} \gg k_4[B]$; the lower addition enthalpy determines in this case higher values of k_{-1} and k_{-3}, allowing the achievement of a steady-state concentration of the benzyl radical suitable for irreversible dimerization, which is characterized by a diffusion-controlled rate and no substitution product is observed.

With isopropyl and α-THF radicals a significant isotope effect has been observed, indicating that the C-H bond is broken in a rate-determining step. The results suggest that the terms $k_2[B]$ and $k_4[B]$ are in these cases comparable, respectively, to k_{-1} and k_{-3} and the rate depends on $[B]$ in non linear way. Under nonlinear catalysis, small changes in the reacting system can have large effects on the kinetics. Thus the solvent and the base catalysis can influence the reversibility of the radical addition (the terms $k_2[B]$ and $k_4[B]$), which can be one of the factors influencing the general behaviour.

The isotope effect indicates that the reversibility is higher in water than in benzene or THF; it appears that the poorly solvated radical ion pair in benzene (eq. 10) irreversibly loses the proton from the C-H bond faster than the

solvated radical ion in water (eq. 11)



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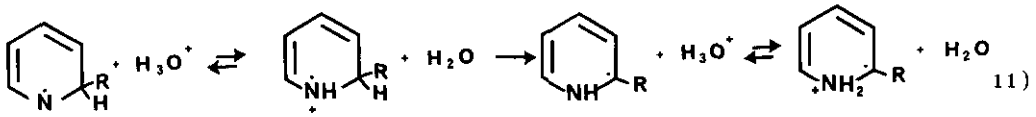
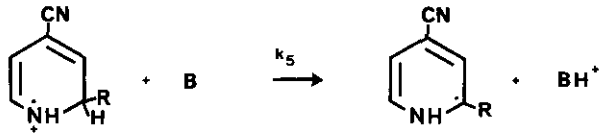


(11)

The results of Table 6 show that the relative rates, determined by the competitive method, between lepidine and 4-cyanopyridine are dramatically influenced by the solvent. Water strongly increases the rate of 4-cyanopyridine relative to lepidine compared *with benzene, toluene or* THF.

Certainly the different equilibria of protonation (4-cyanopyridine is less basic than lepidine) are an unfavourable factor for the alkylation of 4-cyanopyridine in organic solvents. The fact, however, that also with a large excess *of acid in organic solvents* the relative rates are quite different from those obtained in aqueous solution suggests that other factors must be significant. The reversibility and the solvation of polar transition states influence in water more the alkylation of 4-cyanopyridine, which has higher electron deficiency, than the alkylation of lepidine. The higher acidity of the α-C-H bond makes less reversible the radical addition to 4-cyanopyridine in water (eq. 12) (higher value of k_5 compared with the corresponding rate constant for lepidine).



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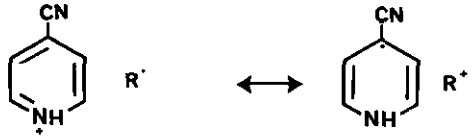
Moreover, the solvation of a more polar transition state (eq. 13) contributes to determine a higher reactivity of 4-cyanopyridine in water.



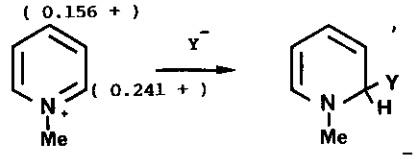
(13)

TABLE 6 - Relative rates in the competitive alkylation of 4-cyanopyridine (k_1) and lepidine (k_2) [13a]

Radical	Solvent	T°C	k_1/k_2
t-Bu	H_2O	80	>100
t-Bu	Benzene	80	0.28
$PhCH_2$	H_2O	80	>100
$PhCH_2$	Toluene	80	0.68
α-THF	THF:H_2O (1:1)	65	1.82
α-THF	THF	65	<0.01

d) Overlap area between nucleophilic radical and ionic nucleophile substitutions of pyridinium ion

The results of the previous sections clearly show a general analogy with the addition of ionic nucleophiles to the pyridinium cation (high regioselectivity in the α and γ positions and high chemoselectivity).
Actually these similar, general mechanistic features are more strict. Thus the total electron-deficiency of the pyridinium cation indicates that the charge control will lead to reaction at the α position[18]. This is the case with nucleophiles with low-energy HOMO [19] (eq. 14).



$Y^- = OH^-, NH_2^-, BH_4^-, RMgBr$ (14)

In terms of HSAB (hard and soft acids and bases) Principle the hard nucleophiles (low-energy HOMO) react faster with the α -position, which is harder than the γ position. According to the orbital interactions the hard-hard reaction is fast because of a large coulombic attraction.
However, nucleophiles with high energy HOMO (CN^-, $CH_2=C(O^-)R$, $S_2O_4^{2-}$) attack the γ -position[20]. According to the HSAB Principle, the softer nucleophiles

react faster with the α position, which is softer than the γ position. In terms of frontier orbital theory (FMO) the LUMO of the pyridinium cation has namely the form of that of benzene, but polarized by the nitrogen atom. This polarization has reduced the coefficient at C_3 and the coefficient at C_4 is larger than that at C_2; the frontier orbital term[21] is largest at C_4, where nucleophiles with high-energy HOMO should attack. The soft-soft reaction is fast because of a large interaction between the HOMO of the nucleophile and the LUMO of the γ position.

Now the change of the α/γ ratio with the structure of the alkyl radical in the substitution of protonated pyridine (Table 4) has a strict connection with the regioselectivity above discussed with ionic nucleophiles. The problem can be considered an extension of the HSAB Principle to free-radical reactions when the polar effect is the dominant factor[13a], in the sense that the softness of a nucleophilic radical increases by decreasing the ionization potentials (- SOMO energy) (similarly, the softness of the ionic nucleophiles increases by decreasing the ionization potentials, which are roughly the energies of the HOMOs). Thus the softness of the alkyl radicals in Table 4 increases in the series Me < primary < secondary < tertiary alkyl < dioxanyl < α-THF and therefore the attack to the softer position (γ position of the pyridium ion) increases according to the same sequence.

According to the FMO theory the SOMO of the radical interacts with the LUMOs of the α and γ positions of the pyridinium cation. A higher lying SOMO determines a larger interaction between the SOMO of the radical and the LUMO of the γ position, which has larger coefficient, and therefore a faster reaction in this position. Thus the similarity of behaviour between ionic nucleophiles and nucleophilic radicals is related to the energies of the HOMOs and SOMOs and their interactions with the LUMOs of the pyridinium ion.

In terms of transition state picture this connection can be related to a similar charge-transfer character in the transition states of the interactions of the nucleophilic radicals (eqs. 7 and 13) and the ionic nucleophiles (eq. 15) with the pyridinium ion.

(15)

RECENT SYNTHETIC DEVELOPMENTS IN THE SUBSTITUTION OF PROTONATED HETEROAROMATIC BASES BY NUCLEOPHILIC RADICALS

The high reactivity and selectivity of the addition of nucleophilic carbon-centered radicals to the protonated heteroaromatic rings and the fast rearomatization of the radical adducts, discussed above, are the main factors which arouse the great synthetic interest of the substitution. These two factors allow, in fact, the use of a great variety of radical sources and heteroaromatic bases.

Beginning[3] from 1968 we have successfully utilized several of the most important classes of organic compounds (alkanes, alkenes, alkyl-benzenes, alcohols, ethers, aldehydes, ketones, carboxylic acids, esters, amides, amines, alkyl halides, peroxides, N-chloroamines, oxaziridine etc.) as radical sources.

Practically, all the carbonyl radicals (acyl, carbamoyl, alkoxycarbonyl) and all the alkyl radicals without electron-withdrawing groups at the radical center are suitable for the selective substitution. The alkyl radicals with electron-withdrawing groups at the β position have sufficient nucleophilicity for the selective alkylation of the heteroaromatic bases.

All the heteroaromatic bases, in which at least one α or γ position is free, are reactive towards these substitutions; sometimes also the ipsosubstitution can occur, always in the α and γ positions. The reactivity and selectivity generally increase with the number of heteroatoms in the aromatic cycles and in polycyclic heterocycles. Thus compounds of great biological interest, such as nucleosides, purine bases, pteridines, alkaloids, are particularly reactive towards these substitutions.

We have reported a great deal of results in several reviews[5]. Some recent synthetic developments are described in the following sections.

a) Selectivity with carbonyl radicals

The reaction reflects most of the numerous aspects of the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity. The synthetic advantages and disadvantages are, therefore, opposite. Thus in the electrophilic process the acylation is much more selective than the alkylation, because the introduction of an acyl group deactivates the aromatic ring towards further acylation, whereas the introduction of an alkyl group activates the aromatic ring towards further alkylation favouring the polysubstitution. In the homolytic process the behaviour is opposite: carbonyl groups activate and alkyl groups deactivate the heterocyclic ring. Consequently,

when more than one position of high nucleophilic reactivity (α and γ) is available in the heterocyclic ring the polysubstitution at these positions by carbonyl radicals easily occurs, whereas it is difficult to arrest the reaction at monosubstitution. However, this limitation is much less severe as compared with electrophilic alkylation because in any case only the α and γ positions of the protonated ring are attacked by the carbonyl radicals and, when only one of these positions is free, complete conversions and only monosubstitution are easily obtained in high yields (that is, a carbonyl group is in any case much less activating than the protonated nitrogen).
The monosubstitution by carbonyl radicals is of synthetic interest in many cases.
An approach[22] was developped by taking advantage of the fact that monosubstituted derivatives by the carbonyl groups are always less basic than the starting base and by adjusting the medium acidicy in order that the starting base is, at least in part, protonated and the monosubstituted derivative is unprotonated. The protonated species is much more reactive and monosubstitution can be effected with good selectivity. This approach is actually difficult to generalize in homogeneous medium because of the large changes of basicity and reactivity of the starting base and the substituted products. This difficulty has been elegantly overcome by G. Heinisch[23] for the alkoxycarbonylation and, with less efficiency, by D. Williams[24] for the acylation by applying a two-phase system procedure.
Table 7 illustrates the results obtained in the alkoxycarbonylation by the redox decomposition of the ethyl pyruvate peroxide[25] by using a two-phase system (water and CH_2Cl_2).

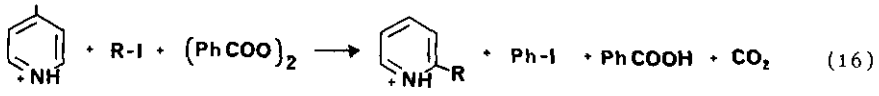
TABLE 7 - Monosubstitution in homolytic ethoxycarbonylation of heteroaromatic bases in a two-phase system (water:CH_2Cl_2)[23]

Heteroaromatic base	Yields (%) of monosubstitution	Orientation
4-Cyanopyridine	85	2
4-Methoxycarbonylpyridine	83	2
4-t-Butoxycarbonylpyridine	90	2
Pyrazine	89	2
Pyrimidine	54	4
4-Ethoxycarbonylpyridazine	74	5

Also these results are based on the different basicity and on the protonation equilibria between the starting bases and the reaction products, but the presence of the organic solvent (CH_2Cl_2) makes easier and more general the process by extracting the less basic unprotonated product of the reaction. The monoalkoxycarbonylation is favoured by the solubility in water of the radical source (pyruvate peroxide). The improvement of the monoacylation by aldehydes[5] in a two-phase system is more limited and moderate, due to the low solubility of the aldehydes in aqueous medium (it gives reasonable results only with the lower aldehydes, which have some solubility in water).

b) Alkyl iodides as sources of alkyl radicals

The relatively low dissociation energy of the C-I bonds makes alkyl iodides particularly useful and general sources of alkyl radicals.
At first we used aroylperoxides and diazonium salts to generate alkyl radicals from alkyl iodides in alkylation of heteroaromatic bases[26] (eqs. 16 and 17).



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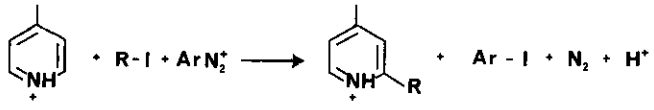


(17)

The mechanism is the general one discussed above. The key step is the fast and selective iodine abstraction from alkyl iodides by aryl radicals (eq. 18) generated from aroyl peroxides or diazonium salts.

$$R\text{-}I + Ar\cdot \xrightarrow{k} R\cdot + Ar\text{-}I \quad . \qquad k > 10^9\ M^{-1}s^{-1} \qquad (18)$$

Although both reactions gave good results in many cases (Table 8), some limitations are encountered with both radical sources.
Aroyl peroxides do react with t-alkyl iodides, but do not produce t-alkyl radicals due to participation in competitive ionic reactions. Moreover the thermal or induced decomposition of aroyl peroxides at first produce aroyloxy radicals, ArCOO, which react with several substrates (activated aromatics, olefins, alcohols, ethers, amines) instead of generating aryl radicals by decarboxylation.

The main limitation encountered with diazonium salts is due to the high addition rates of the nucleophilic radicals to the diazonium group, leading to the "free-radical diazo-coupling reaction" [27] (eq. 19).

$$R\cdot + N \equiv \overset{+}{N}\text{-Ar} \longrightarrow R\text{-}\overset{+}{N}\text{=}\dot{N}\text{-Ar} \xrightarrow{+e} R\text{-N=N-Ar} \qquad (19)$$

This competition can be in part restricted by keeping low the stationary concentration of the diazonium salt during the reaction.

TABLE 8 - Alkylation of heteroaromatic bases by diazonium salt, benzoyl peroxide and alkyl iodides[11]

Heteroaromatic base	Radical source	Alkyl iodide	Orientation	Yield % [a]
Quinaldine	ArN_2^+	i-PrI	4	96
"	"	c-$C_6H_{11}I$	4	91
Lepidine	"	"	2	95
"	"	n-BuI	2	98
"	"	t-BuI	2	76
Quinoline	"	c-$C_6H_{11}I$	2(44%)4(56%)	93
Isoquinoline	"	"	1	90
4-Cyanopyridine	$(PhCOO)_2$	n-BuI	2(66%)2.6(34%)	100
"	"	i-PrI	2(75%)2.6(25)	96
Isoquinoline	"	EtI	1	85
"	"	c-$C_6H_{11}I$	1	92
Quinaldine	"	"	4	88
"	"	n-BuI	4	93
"	"	i-BuI	4	98
Lepidine	"	c-$C_6H_{11}I$	2	95
"	"	n-BuI	2	93
"	"	i-BuI	2	98
"	"	$I(CH_2)_2COOEt$	2	93
Acridine	"	c-$C_6H_{11}I$	9	94
Benzothiazole	"	i-PrI	2	90

a) Based on converted base; conversions (30-100%) can be increased by increasing the amount of the radical source.

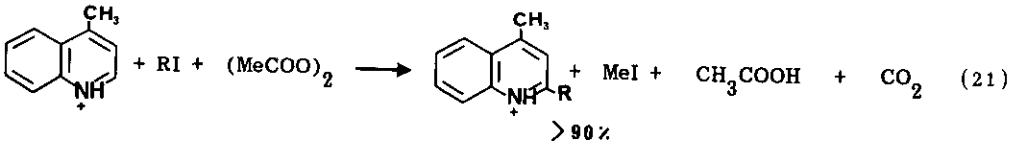
To overcome these difficulties we have recently developped a new general pro-

cedure for generating alkyl radicals by means of the iodine abstraction from alkyl radicals with methyl radical[28] (eq. 20).

$$R\text{-}I + Me\cdot \rightleftharpoons R\cdot + Me\text{-}I \qquad (20)$$

Combined enthalpic and polar factors make this process particularly versatile for the heteroaromatic substitution. The enthalpic factor governs the equilibria of eq. 20, which are always shifted to the right, and the polar factor governs the selectivity of the alkyl radical reactions with heteroaromatic bases.

The following simple and cheap sources of methyl radical proved of useful for the selective alkylation of heteromatics with alkyl iodides (eqs. 2 -26).



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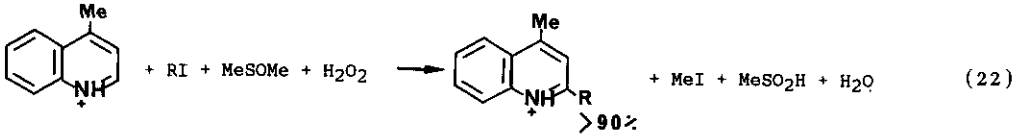

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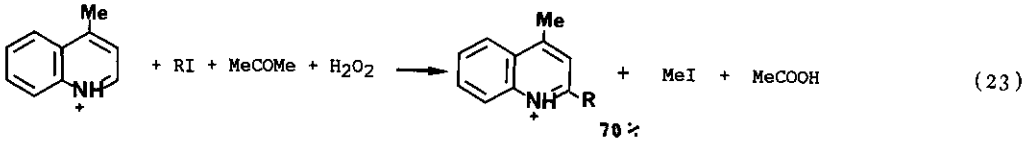
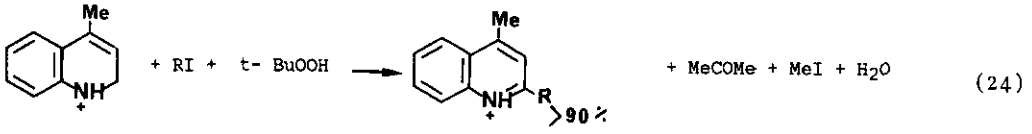


(23)



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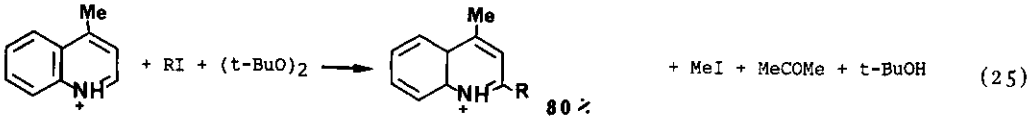

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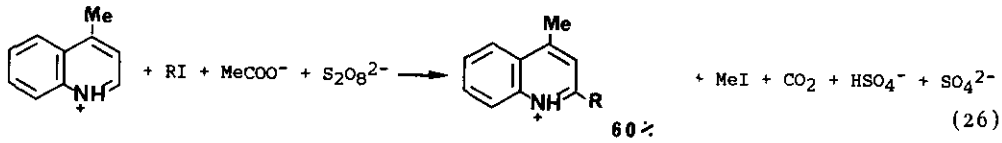
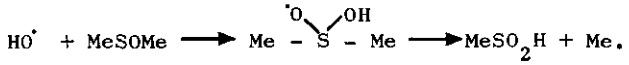


(26)

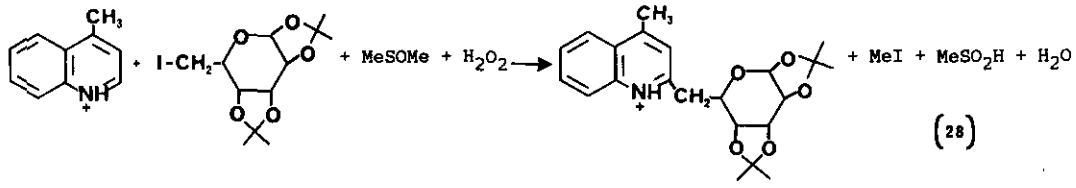
The advantage of using $(MeCOO)_2$ compared with $(PhCOO)_2$ is owing to the fact that the radical MeCOO. decarboxylates much faster than ArCOO•, the limitations encountered with $(ArCOO)_2$ being avoided. The disadvantage is due to the fact that $(MeCOO)_2$ is not a commercial product because of its dangerousness. However, solutions of $Me(COO)_2$ in MeCOOH can be easily prepared from Ac_2O and Na_2O_2 and these solutions can be utilized with safety for the heteroaromatic substitution.

The procedure of eq. 22, catalyzed by Fe(II) salt, is also very versatile because the high reactivity and low selectivity of the HO• radical with a large variety of organic and inorganic compounds are controlled by using DMSO (eq. 27) and the possible, fast, unselective and competitive reactions with other substrates are minimized by the excess of solvent. The radical adduct selectively undergoes β-scission, acting thus as selective source of Me• radical.



(27)

In this way complex substrates, such as iodosugars, can be also utilized with good selectivity. For example, 6-iodo-1,2,3,4-diisopropyliden-α-galactose reacts with lepidine giving selectively the corresponding C-nucleoside[28] (eq. 28)



(28)

Since a large variety of iodosugars is available and the secondary iodides are more reactive and selective than primary alkyl iodides, this new method seems particularly suitable for the synthetic approach of C-nucleosides with

heteroaromatic bases, including purine bases, of great interest for the biologycal activity (i.e. tiazofurin and selenoazofurin). The procedure of eq. 23 is also particularly simple and the methyl radical is generated by the acetone peroxide formed in situ (eq. 29).

$$2\ MeCOMe + H_2O_2 \rightleftharpoons Me_2\underset{OH}{C} - O-O-\underset{OH}{C}Me_2 \longrightarrow 2\ Me\underset{OH}{C} - O\cdot \longrightarrow 2\ Me\cdot + 2MeCOOH \quad (29)$$

In the procedure of eqs. 24 and 25 the methyl radical is generated from t-BuO· radical (redox or thermal decomposition of the peroxides) (eq. 30).

$$Me_3CO\cdot \longrightarrow MeCOMe + Me\cdot \quad (30)$$

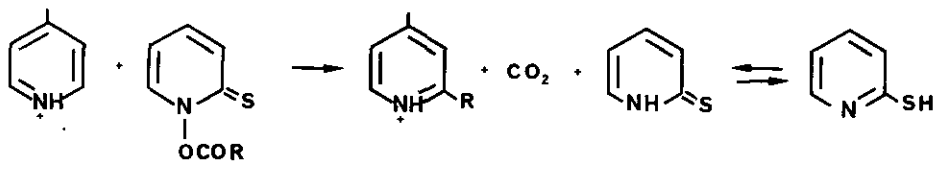
The procedure of eq. 26 is less versatile, due to the sparing solubilities of the persulphate and the alkyl iodide in the reaction medium.
Pyrilium salts can be also selectively alkylated by use of these radical sources.

c) Alkylation by carboxylic acids

The oxidative decarboxylation of carboxylic acids is a quite general route to carbon-centered radicals (eq. 31), useful for the heteroaromatic substitution

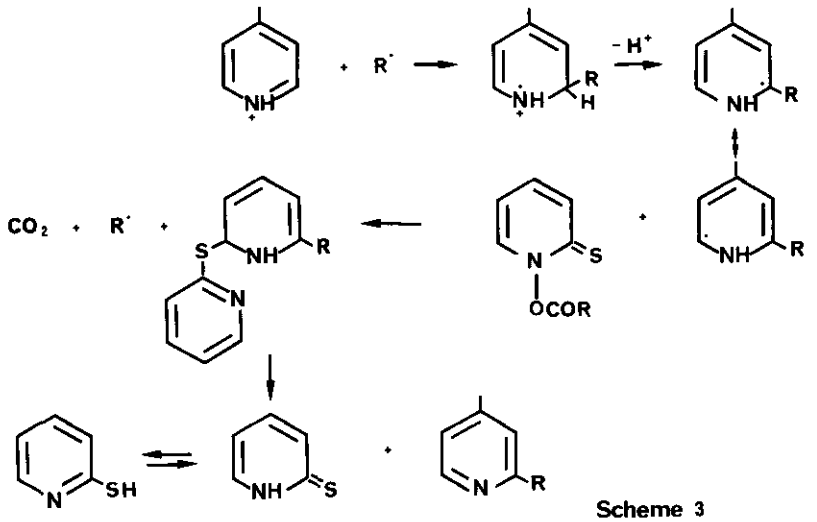
$$RCOOH \xrightarrow{-e} R\cdot + CO_2 + H^+ \quad . \quad (31)'$$

A large variety of chemical or electrochemical oxidation have been utilized[5]. Generally the method of choice is the decarboxylation by persulphate for the simplicity, the cheap oxidant and the high yields[5]. In this case the problem of solubility is not a limiting factor, because a small solubility of the carboxylic acid in water or in mixtures of water and organic solvents is sufficient for the reaction to proceed effectively. The oxidation can be mediated by silver salt catalysis. Recently we have reported[29] that the silver catalysis is effective also with peroxycarbonate, which can be useful when particular problems of solubility make less effective the use of persulphate.
A recent new procedure has been developped by Barton and coworkers[6]; it is based on the free-radical decomposition of thiohydroxamic esters (eq. 32).



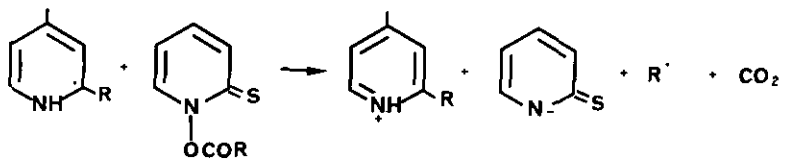
(32)

A free-radical addition-elimination chain process has been suggested (Scheme 3).



Scheme 3

However, an electron-transfer mechanism (eq. 33) is another possible explanation, taking into account the high reducing character of the pyridinyl radical and the fact that hydroxylamine-O-sulphonic acid, NH_2OSO_2H, oxidizes very effectively the pyridinyl radicals.

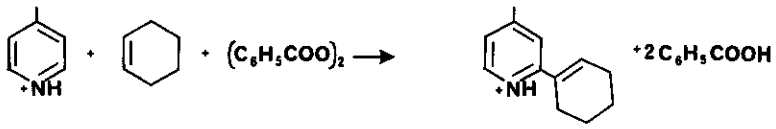


(33)

Manifestly this method is much more complex and expensive than those previously developped by us, but it can be useful in those cases in which the substrates have a particular sensitity to the utilized oxidants.

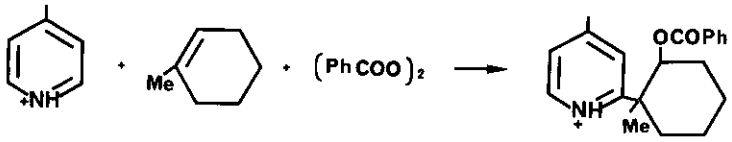
d) Vinylation and β-oxyalkylation by olefins

The decomposition of benzoyl peroxide in the presence of olefins leads to vinylation of the protonated heteroaromatic bases[30] (eq. 34).



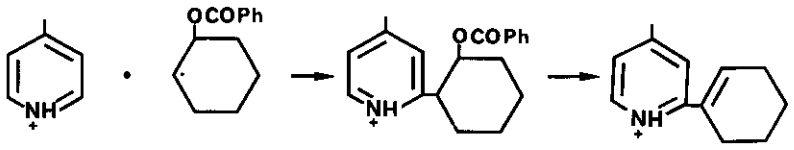
(34)

The result with 1-methylcyclohexene (eq. 35) makes clear the reaction mechanism.



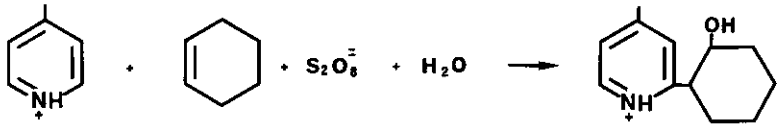
(35)

The benzoyloxy radical, PhCOO• , adds to the olefin and this radical adduct alkylates the base, followed by elimination of benzoic acid (eq. 36).



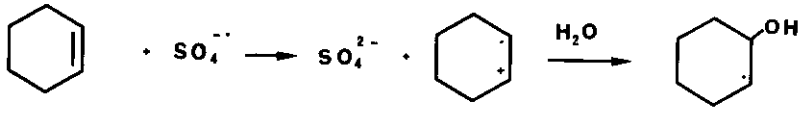
(36)

With 1-methylcyclohexene the elimination of benzoic acid is not structurally possible and the intermediate ester is obtained. The process is similar to the hydroxyalkylation by olefins and persulphate[31] (eq. 37).



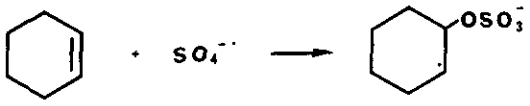
(37)

The formation of the hydroxycyclohexyl radical has been interpreted via a radical cation intermediate (eq. 38).



(38)

The recent results of Steenken[32] suggest that the addition of the sulphate radical anion to the olefin (eq. 39), followed by the hydrolysis of the sulphonic ester, cannot be excluded.

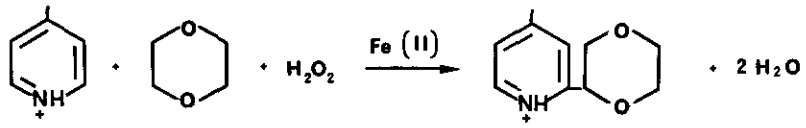


(39)

A radical cation is more probable, when the reaction is catalyzed by Ag(I) salt.

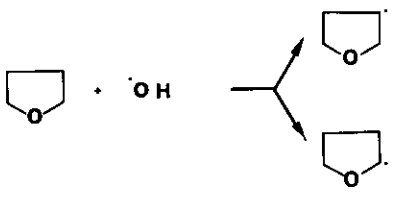
e) <u>α-Oxyalkylation by cyclic ethers and H_2O_2</u>

The hydroxyl radical generated by the redox decomposition of hydrogen peroxide can be utilized for the α-oxyalkylation of heteroaromatic bases (eq. 40).



40)

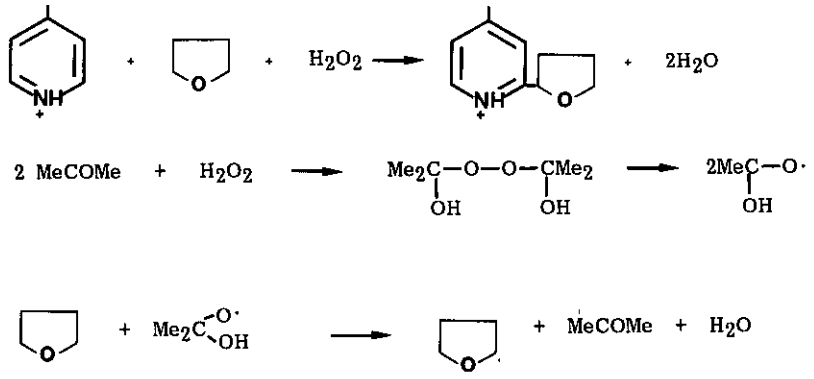
The main synthetic limitation of this procedure is the low regio and chemoselectivity of the hydrogen abstraction by the hydroxyl radical. In the *case of dioxane, trioxane or some crown* ethers in which only one kind of C-H bond is present, good results were obtained because there is no problem of regioselectivity and the low chemoselectivity has been overcome by using an excess of ether[33]. However, when more than one kind of C-H bonds are present, as in THF, the hydrogen abstraction is not selective: two different radicals (eq. 41) are formed and both have sufficient nucleophilic reactivity toward the heteroaromatic substitution.



(41)

To overcome this limitation we have developped a simple procedure in which the hydrogen peroxide is utilized in acetone solution, in the absence of

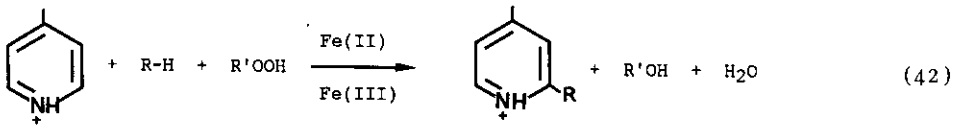
metal salt catalysis[34] (Scheme 4). In this way a good selectivity of the hydrogen abstraction occurs from the C-H bonds in position α to the oxygen of the ether because a more selective abstracting species is involved.



Scheme 4

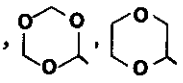
f) Catalytic processes in the substitution by nucleophilic radicals

Important substitution reactions, such as hydroxymethylation[33], formylation[35], carbamoylation[22c], dioxanylation[33], α-N-amido-alkylation, and acylation[33], have been achieved by very trivial reagents, such as methanol, formaldehyde, formamide, dioxane, THF, DMF, N-methylacetamide, and aldehydes according to the general scheme (eq. 42).



(42)

R' = H or t-Bu R- = $-CH_2OH$, $-CHO$, $-CONH_2$, $R''CO-$, $CHON(Me)CH_2-$,



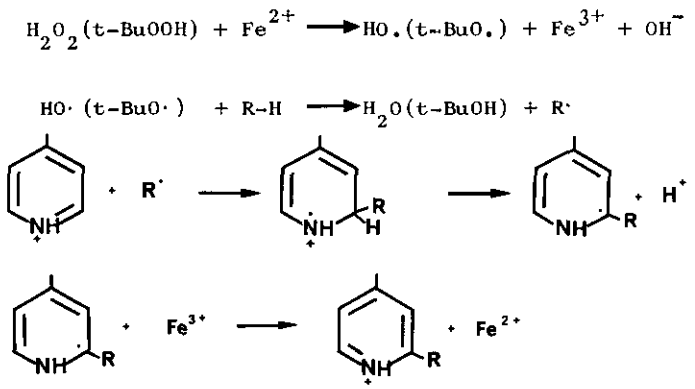
All these reagents can be used without problems in large excess as solvent, thus minimizing the low chemoselectivity of the hydrogen abstraction by hydroxy and alkoxy radicals involved in the reaction. In our previous studies we have utilized stoichiometric redox systems H_2O_2/Fe^{2+} and t-BuOOH/Fe^{2+} at room temperature to generate HO• and t-BuO• radicals and some limitations occur.

The mechanistic consideration of the reaction has allowed us to make these

substitutions highly catalytic with considerable improvements.
All the radicals of eq. 42 have an enhanced nucleophilic character due to the α nitrogen or oxygen atoms. Now, the increased nucleophilic character is generally associated with the increased stability and oxidability of the radicals R. involved. On the other hand, the increased stability is reflected in a lower enthalpy and consequent higher reversibility of the radical addition to the heterocyclic ring. With stoichiometric redox systems the conversions were sometimes low, due to the high concentration of Fe(III) salt, which by fast oxidation of the radical R. (i.e. eq. 43) shifts the equilibria of the Scheme 2 to the left.

$$.CH_2OH + Fe^{3+} \xrightarrow{x} CH_2O + H^+ + Fe^{2+} \qquad k>10^8\ M^{-1}s^{-1} \qquad (43)$$

Since pyridinyl type radicals are involved in the rearomatization step, we realized that a small concentration of Fe(III) salt should be sufficient for a fast and selective rearomatization of the radical adducts minimizing the reversibility and the competitive reactions such as eq. 43.
Thus we have developped new procedures, combining thermal and redox processes, which are very efficient and require only catalytic amounts of iron salt (Fe(II) and Fe(III) are equally efficient). The redox chain of the Scheme 5 is operating.



Scheme 5

At room temperature with Fe(III) salt no reaction occurs and only traces of substitution products are formed in the presence of catalytic amount of Fe(II) salt. Without iron salt, no substantial reaction occurs even at higher temperatures. This means that at room temperature the kinetic chain of the Scheme 5 is short, due to the fast oxidation of Fe(II) salt (eq. 44),

which breaks the chain.

$$Fe^{2+} + \cdot OH \longrightarrow Fe^{3+} + OH^- \qquad (44)$$

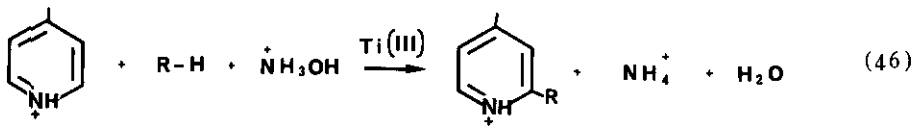
The initiation step with Fe(III) salt appears to follow eq. 45.

$$HOOH(t\text{-}BuOOH) + Fe^{3+} \longrightarrow HOO\cdot(t\text{-}BuOO\cdot) + H^+ + Fe^{2+} \qquad (45)$$

This step is relatively slow and requires temperatures higher than 50°C (generally 70-100°C) to be efficient. Moreover, eq. 45 is much slower than the steps of the redox chain leading to the heteroaromatic substitution (Scheme 5) so that the stationary concentration of Fe(II) salt remains very low during the reaction, minimizing the reaction 44.
In this way good results can be obtained (Table 9).
A further advantage is that the catalytic procedure is much simpler because the small amount of iron salt does not interfere with the isolation of the reaction products, whereas with stoichiometric iron salt considerable amounts of $Fe(OH)_3$ precipitate during the separation of the basic reaction products (sometimes complexing the heterocyclic compounds), heavily affecting the overall process.
These processes for the general character, the high yields and selectivities, the cheap reagent and catalyst, the simple experimental conditions, the interest of the reaction products are suitable also for practical applications[36].

g) Substitution by strongly nucleophilic radicals. Amino radicals as precursors of carbon-centered radicals

Redox chains similar to that described in the Scheme 5 were obtained by utilizing amino radicals from hydroxylamine[22c] and hydroxylamine-O-sulphonic acid[37] instead of hydroxy and alkoxy radicals (eqs. 46 and 47).



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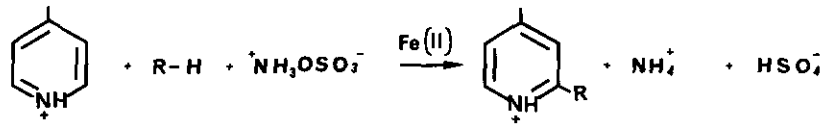


(47)

TABLE 9 - Catalytic substitution of heteroaromatic bases

$Ar-H + R-H + R'OOH \longrightarrow Ar-R + R'OH + H_2O$

ArH	R-H	R'OOH	Orientation	Yield %[a]	Ref.
Quinoline	$HCONH_2$	HOOH	2,4-Disubstituted	97	22c
Quinoxaline	"	"	2	88	"
Isoquinoline	"	"	1	100	"
Acridine	"	"	9	82	"
Benzothiazole	"	"	2	68	"
Lepidine	"	"	2	99	"
"	"	t-BuOOH	2	93	"
Quinoline	Trioxane	"	2(58%) 4 (42%)	92	35
Quinaldine	"	"	4	94	"
Isoquinoline	"	"	1	92	"
Quinoxaline	"	"	2	94	"
Benzothiazole	"	"	2	90	"
Lepidine	"	"	2	94	"
"	"	HOOH	2	93	"
"	Dioxane	"	2	90	33
"	"	t-BuOOH	2	95	"
"	Methanol	"	2	99	"
"	"	HOOH	2	95	"
"	Benzaldehyde	t-BuOOH	2	75	"
Acridine	"	"	9	70	"
2-Cyanoquinaline	"	"	4	75	"

a) Based on converted base; conversions (40-100%) can be further increased by increasing the amount of hydroperoxide.

Particularly eq. 46 can be synthetically useful with strongly nucleophilic radicals, for which the presence of the redox couple Fe(II)/Fe(III) is not compatible. Thus the catalytic process described by the Scheme 5 gives good

results in hydroxymethylation by methanol, but not in α-hydroxyethylation by ethanol. Two main factors contribute to determine this behaviour:

i) The faster oxidation of the radical $Me\dot{C}HOH$ by Fe(III) salt (eq. 48) (practically controlled by the diffusion) compared to that of $\cdot CH_2OH$.

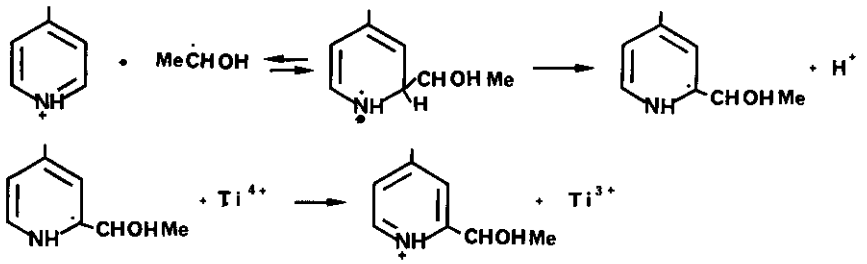
$$Me\dot{C}HOH + Fe^{3+} \longrightarrow MeCHO + H^{+} + Fe^{2+} \qquad (48)$$

ii) The higher reversibility of the addition of the radical $Me\dot{C}HOH$ to the heterocyclic ring.

Hydroxylamine and Ti(IV) salt are very mild oxidizing species and good results were obtained[22c] also by ethanol according to the redox chain of the Scheme 6 .

$$\overset{+}{N}H_3OH + Ti^{3+} + H^{+} \longrightarrow \dot{\overset{+}{N}}H_3 + Ti^{4+} + H_2O$$

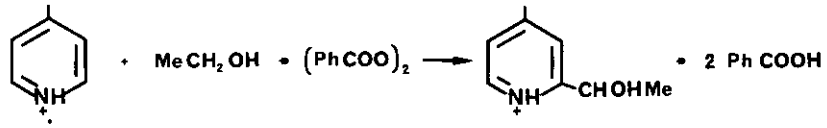
$$\dot{N}H_3 + MeCH_2OH \longrightarrow \overset{+}{N}H_4 + Me\dot{C}HOH$$



Scheme 6

This procedure has been suggested by the awareness that a mild oxidant, such as Ti(IV) salt, can still fast and selectively oxidize the pyridinyl type radical. At the same time the oxidation of the radical $Me\dot{C}HOH$ by Ti(IV) is much slower than the oxidation by Fe(III) salt and that contributes to shift the equilibrium in the Scheme 6 to the right.

Good results of α-hydroxyethylation were also obtained[22c] by using benzoyl peroxide to generate the radical $Me\dot{C}HOH$ (eq. 49). Also in this case the results were explained by the relatively slow oxidation of the radical $Me\dot{C}HOH$ (eq. 50) and the fast oxidation of the pyridinyl radical (Scheme 1) by the benzoyl peroxide.



(49)

$$MeCHOH + (PhCOO)_2 \longrightarrow MeCHO + PhCOOH + PhCOO\cdot \qquad (50)$$

CONCLUSION

A deep understanding of the mechanism of the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals (particularly kinetics and equilibria) has allowed to develop new synthetic potentialities, which contribute to make the general reaction one of the most important of this class of heterocyclic compounds.

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