Substitutions by Nucleophilic Free Radicals: A New General Reaction of Heteroaromatic Bases

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The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals has been developed as one of the most general reactions in the heterocyclic series; its great interest 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 developments, concerning the generation of free radicals by iodine and hydrogen abstraction and decarboxylation of carboxylic acids are particularly discussed. Some processes of high synthetic value were designed on the basis of the kinetic and thermodynamic features of all the elementary steps involved in complex but selective chain processes. New general procedures for the monosubstitution in the homolytic alkylation and acylation are reported and discussed.

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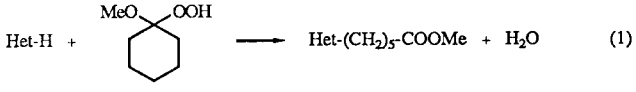
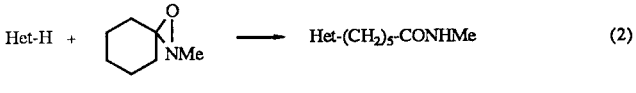
Introduction.

In 1968 we [1] have shown that selective substitutions could be realized by reactions of nucleophilic carbon-centered radicals with electron-deficient substrates. Electron-poor olefins [2] and heteroaromatic bases [3] were revealed to be particularly interesting for the synthetic involvements. Cyclohexanone peroxide, obtained by simply mixing cyclohexanone and hydrogen peroxide in methanol, and *N*-methylpentamethyleneoxazirane (from cyclohexanone and *N*-chloromethylamine) were at first utilized as radical sources (equations 1 and 2).





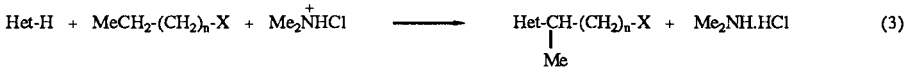
Het-H = pyridine, quinoline, isoquinoline, pyrazine, acridine, pyrimidine, benzothiazole

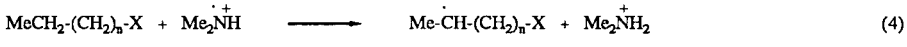
The great synthetic potentiality of this kind of substitution clearly resulted by the exceptional regio- and chemoselectivity. We [3] soon realized that the high selectivity was due to polar effects and that it was strictly related to the nucleophilic character of carbon-centered radicals.

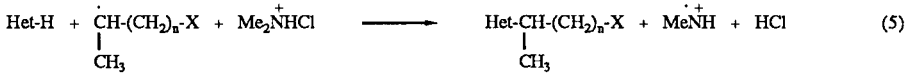
The origin of this rationalization and of the further developments in this area was conceptually derived from our previous results [4] concerning the reactivity of protonated amino radicals, $^{\cdot}R_2NH$, with alkanes, alkenes and aromatics. The high selectivity was due, in these cases, to the strong electrophilic character of $^{\cdot}R_2NH$. Thus, a very small difference in the electron availability between two substrates or different positions in the same substrate is reflected by a high selectivity [4] of the reactions with $^{\cdot}R_2NH$. The fundamental idea derived from the awareness [5] that the overall polar effect in free-radical reactions is the result of polarity and polarizability of both the radical and the substrate, which means that the polarity of the substrate is not less important than the polarity of the radical in determining the sensitivity to polar effects. We strongly increased the polar character of the amino radicals by protonation; with heteroaromatic bases the polarity of the carbon radicals is generally low, but the polarity of the substrates is strongly increased, always by protonation. The overall selectivity, resulting from polar effects, is however very high in both cases.

The combination of these two exceptional polar effects is shown [6] by equation 3, in which the electrophilic character of the protonated amino radical determines the selective hydrogen abstraction (equation 4) and the resulting nucleophilic carbon-centered radical selectively reacts with the protonated heteroaromatic base (equation 5) in a chain process.

Actually the reactions of equations 1 and 2 became important from a synthetic point of view only in acidic medium



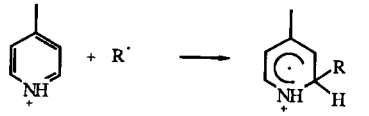




X = electron withdrawing group (Cl, $\overset{+}{N}R_3$, COOR, CN, COR, NO_2 *etc.*); n = 2-6

(with protonated bases); in non-acidic medium the same reactions have a very poor interest because either they do not take place or they occur in low yields and with very low regio- and chemo-selectivity. Heteroaromatic bases are electron-deficient aromatic substrates which readily react with nucleophilic species. The protonation strongly increases their electron-deficient nature and therefore the reactivity towards nucleophilic reagents. Thus, treating the heterocyclic nitrogen atom of pyridine as a substituent in the benzene ring, the exceptionally high value of 4 was estimated for the σ-Hammett constant of the *p*-position in the protonated pyridine [7], the corresponding value of the unprotonated pyridine [8] being 0.93. The increased nucleophilic reactivity of protonated hetero-aromatic bases cannot be mostly exploited with ionic nucleophilic species, which cause the deprotonation of the base as a primary effect. This incompatibility does not occur with nucleophilic radicals; this made it possible to take advantage of the increased nucleophilic reactivity following protonation in order to develop a large variety of substitutions, characterized by high regio- and chemoselectivity, and consequently great synthetic interest. They reproduce most of the numerous aspects of the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity owing to the nucleophilic characters of the radicals. The homolytic substitutions can also be divided, in a generalized sense, into alkylations and acylations, which include considerably different reactions. The polar effect is, in fact, reflected in transition states more similar to charge-transfer complexes [3] (equation 6) than to radical adduct intermediates (equation 7).

(6)



(7)

The parallelism with Friedel-Crafts substitutions is, therefore, related to the fact that, generally, the more stable the carbonium ion is, the more nucleophilic the corresponding radical will be (equation 6). Thus, in principle, all the electrophilic species useful in the Friedel-Crafts reaction can be utilized, as corresponding radicals, for the selective substitution of heteroaromatic bases. Practically all the carbon-centered radicals are suitable with the same exceptions observed for the electrophilic process: the electron-withdrawing groups bonded to the potential reactive center inhibit both the homolytic substitution, because of the decreased nucleophilic character of the radical, and the electrophilic process, because of the difficulty to develop an incipient positive charge.

The high reactivity and selectivity of addition of nucleophilic carbon-centered radicals to the protonated heteroaromatic ring have allowed us to successfully utilize, starting from 1968, a large variety of radical sources, involving several of the most important classes of organic compounds. Practically all the carbonyl (acyl, carbamoyl and alkoxycarbonyl) and the alkyl radicals without electron-withdrawing groups directly bonded to the radical center can be successfully utilized. All the heteroaromatic bases, including compounds of great biological interest, such as nucleosides, purine bases, pteridines etc., in which at least one α or γ position is free, are suitable for selective substitution. The dominant role of polar effects is shown by the influence of the substituents [9]: electron-withdrawing groups activate and electron-releasing groups deactivate the heterocyclic ring. However, a thorough examination [10] of the reaction mechanism indicates that the relative rates determined by the competitive method have only a qualitative meaning, because the addition of carbon radicals to the heterocyclic ring is mostly reversible and the relative rates can be dramatically influenced by the solvent. We have reported a great deal of mechanistic and synthetic results in several reviews [3]. In this lecture we will particularly discuss recent results concerning the use of iodine and hydrogen abstraction and of decarboxylation of carboxylic acids for generation and synthetic applications of nucleophilic carbon-centered radicals and also the general problem of selective monosubstitution in acylation and alkylation when more than one position of high nucleophilic reactivity (generally α and γ) are available in the heterocyclic ring.

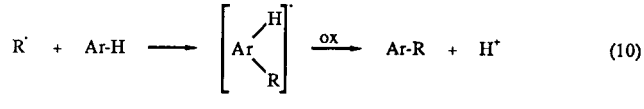
Iodine and Hydrogen Abstraction as Sources of Alkyl and Acyl Radicals.

Alkyl iodides have been largely utilized as sources of alkyl radicals by iodine abstraction under reductive conditions [2b]: organometallic radicals (i.e. $R_3Sn^{\cdot}$) (equation 8) or reducing metal salts (equation 9) proved to be particularly useful.

$$R + {}^{\cdot}SnR_3 \longrightarrow R^{\cdot} + I\text{-}SnR_3 \qquad (8)$$

$$R\text{-}I + Cr^{2+} \longrightarrow R^{\cdot} + Cr^{3+} + I^{-} \qquad (9)$$

High rates make reactions (8) and (9) very selective; they have been successfully utilized to reduce alkyl iodides or for the reductive alkylation of unsaturated substrates in chain processes [2b]. These selective sources of alkyl radicals, however, are not suitable for the aromatic substitution, characteried by oxidative alkylation (equation 10).



(10)

To be useful for heteroaromatic substitution, the radical source must have oxidative character; therefore, we have considered different approaches based on iodine abstraction from alkyl iodides by aryl (equation 11) or methyl (equation 12) radicals, generated under oxidative conditions.

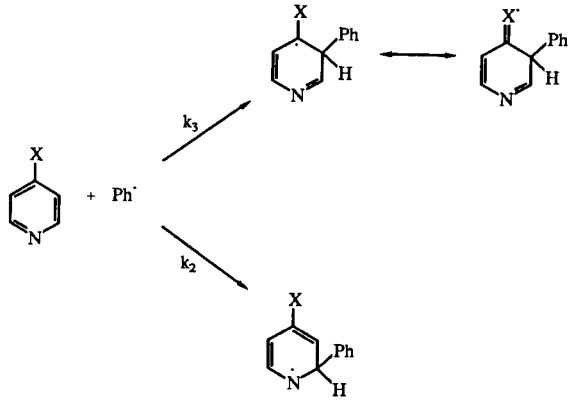
$$R\text{-}I + Ar^{\cdot} \longrightarrow R^{\cdot} + Ar\text{-}I \qquad (11)$$

$$R\text{-}I + Me^{\cdot} \longrightarrow R^{\cdot} + Me\text{-}I \qquad (12)$$

The design of effective chain processes of large synthetic interest was based in these cases on the knowledge or evaluation of rates and equilibria of all the elementary steps involved in the chains. For synthetic purposes it is not necessary to know the exact values of rate constants: only a knowledge of their order of magnitude is required; a different of one order of magnitude between the rate constants of two competitive processes is sufficient to obtain a selective process,

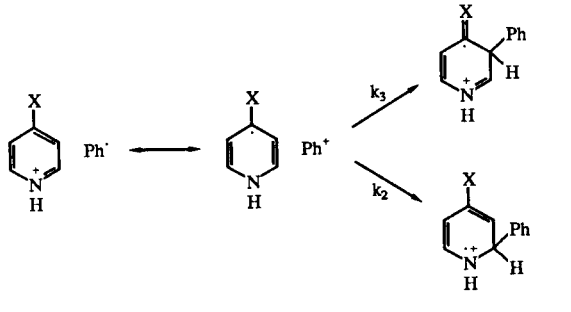
through opportune modulation of the relative concentrations of the reagents. This knowledge is much more important in free radical than in ionic reactions, as rates are seldom affected to a macroscopical extent by the reaction medium in free-radical reactions, contrarily to the behaviour of ionic reactions. Now phenyl, and in general aryl, radicals are considered highly reactive, unselective radicals in agreement with the reactivity-selectivity principle (RSP) [11]. Moreover, the polar effect of the phenyl radical is generally considered negligible (a ρ value close to zero has been reported [12] for the substitution of benzene derivatives). However, we [13] have reported evidence that, while the RSP is a valid criterion for free-radical processes when the reaction enthalpy mainly governs the reactivity, it may be reversed when polar effects play a dominant role.

Moreover, we [14] have expressed the concept that the polar effect, being kinetic in nature, is not an intrinsic property of a free radical and that it is not correct to attribute a defined polar character to a given radical without taking into account the particular type of reaction involved. Thus we determined the absolute rate constants for the homolytic phenylation of protonated and unprotonated 4-substituted pyridines [15]. The results of Table 1 show that the phenyl radical substantially behaves as a nonpolar species in the addition to unprotonated pyridines, but it shows a nucleophilic character in the addition to protonated pyridines, because polar effects also depend on the polarity of substrate. Thus with unprotonated pyridines the reactivity and the regioselectivity appear to be mainly governed by the stability of the intermediate radical adduct (equation 13) and the polar effect is a minor factor, so that it is $k_3 > k_2$ for both electron-withdrawing and electron-releasing substituents. With protonated pyridines polar effects, due to the charge separation in the transition state



(13)

(equation 14), play a significant role in determining reactivity and selectivity. The 2-position, due to its lower electron density, is attacked faster, $k_2 > k_3$ for all the substituents and the phenyl radical shows nucleophilic character.



(14)

This interpretation is supported by the fact that the rates in β-positions remain substantially unchanged, whereas the rates for α-positions are significantly increased by the presence of electronwithdrawing groups in γ-position, where there is no radical stabilizing effect.

Table 1

Absolute Rate Constants ($M^{-1}s^{-1}$ 10^{-6}) for the Homolytic Phenylation of 4-Substituted Pyridines

Substituent	Protonated		Unprotonated	
	2	3	2	3
CN	6.02	3.61	1.22	3.41
Cl	5.23	1.50	0.90	1.43
H [a]	3.67	0.24	0.44	0.25
Me	1.95	0.40	0.32	0.36
MeO	1.19	0.25	0.23	0.38

[a] The position 4 is also attacked ($3.12\ 10^6$ and $0.28\ 10^6$ $M^{-1}s^{-1}$ for protonated and unprotonated pyridine).

Compared to acyl and alkyl radicals, however, polar effects in the phenyl radical reactions are much lower, and that is reflected in much lower regio- and chemoselectivity and consequent synthetic interest. The results of Tables 1 and 2 show that the phenyl radical is much more reactive and much less selective (all the free aromatic positions are attacked) than alkyl or acyl radicals with benzene derivatives and unprotonated pyridines. However, with protonated 4-cyanopyridine, alkyl and acyl radicals are still more selective, but even more reactive than the phenyl radical, with consequent greater synthetic interest.

Table 2

Absolute Rate Constant for the Addition of Carbon-centered Radicals to Aromatics (2-position) ($M^{-1}s^{-1}$)

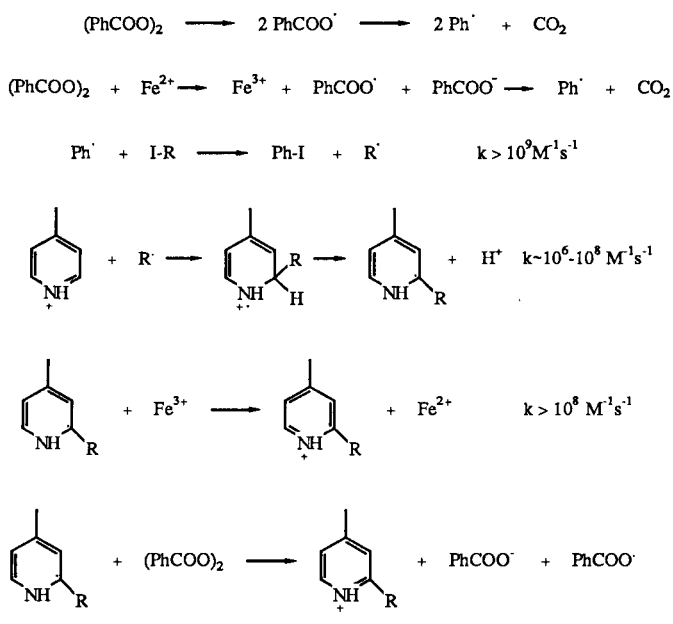
Radical	Benzene	4-Methylpyridine unprotonated	4-Cyanopyridine protonated	Ref
Ph	$1.03\ 10^6$	$0.4\ 10^6$	$6.02\ 10^6$	15
n-Bu	$3.8\ 10^2$	$1.3\ 10^3$	$8.9\ 10^5$	16
t-Bu	no reaction	no reaction	$6.3\ 10^7$	17
t-BuCO	no reaction	no reaction	$> 10^6$	18
CH_2OH	no reaction	no reaction	$> 10^7$	19

The knowledge of the rate constants for the addition of phenyl and alkyl radicals to the heterocyclic ring has allowed us to design a very effective chain process for the homolytic alkylation of protonated heteroaromatic bases by alkyl iodides [15]. We have utilized benzoyl peroxide and diazonium salts as sources of aryl radicals; the stoichiometry with benzoyl peroxide is shown by equation 15.

(15)

A thermal or redox decomposition of the peroxide initiates a free-radical or a redox chain, according to Scheme I.

Scheme I



Some results are shown in Table 3.

Table 3

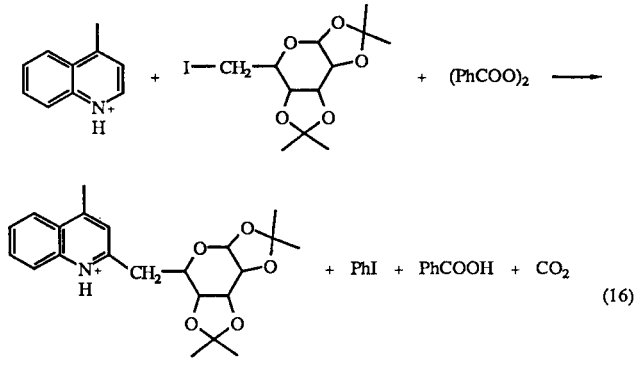
Alkylation of Heteroaromatic Bases by Benzoyl Peroxide and Alkyl Iodides [15]

Substrate	Radical	Position of Substitution (%)	Yields %
4-Cyanopyridine	*n*-Bu	2 (75), 2, 6 (25)	96
"	*i*-Bu	2 (58), 2, 6 (42)	98
"	*i*-Pr	2 (66), 2, 6 (34)	100
Isoquinoline	Et	1 (100)	85
"	Cyclohexyl	1 (100)	92
Quinaldine	Cyclohexyl	4 (100)	88
"	*n*-Bu	4 (100)	93
"	*i*-Bu	4 (100)	98
Lepidine	*n*-Bu	2 (100)	88
"	*i*-Pr	2 (100)	98
"	Cyclohexyl	2 (100)	95
"	$EtOOCOCH_2CH_2$	2 (100)	93
"	2-Hydroxycyclohexyl	2 (100)	85
Acridine	Cyclohexyl	9 (100)	94
Benzothiazole	*i*-Pr	2 (100)	90

[a] Based on converted substrate-conversions 50-100%.

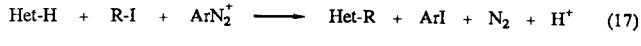
A key point is iodine abstraction by phenyl radical: it occurs at nearly every collision and the rate constant is about three orders of magnitude higher than those for the addition of phenyl radical to aromatic or heteroaromatic derivatives (Tables 1 and 2) and for most of the other possible competitive reactions; this makes the process a particularly selective general source of alkyl radicals. The fast and selective addition of alkyl radicals to heterocyclic rings [16-19] and the fast oxidation of the pyridinyl-type radical adduct, due to its high reducing character [20], contribute to fulfill an effective chain process of large synthetic interest.

Complex substrates, such as iodosugars, have also been utilized with good selectivity; for instance, 6-iodo-1,2,3,4-diisopropylidene-α-galactose reacts with lepidine giving the corresponding *C*-nucleoside [21] (equation 16).



(16)

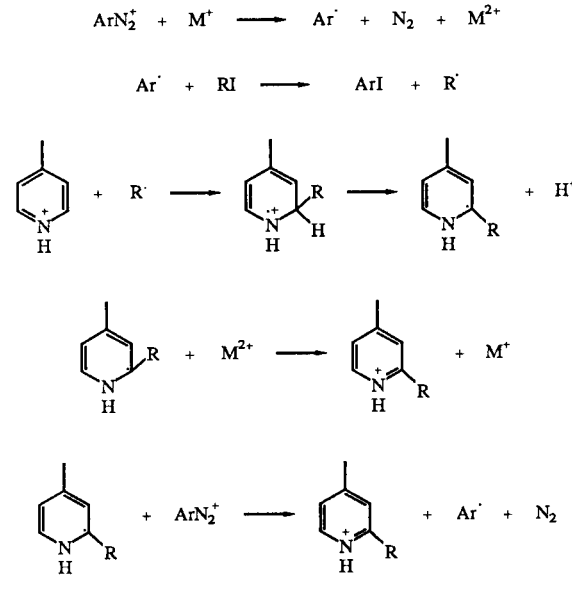
The reaction stoichiometry with diazonium salts is shown by equation 17.



(17)

The chain process (Scheme II) was induced in this case by Fe(II) or Cu(I) salts (M^+).

Scheme II



Some results are reported in Table 4.

Table 4

Alkylation of Heteroaromatic Bases by *p*-Chlorobenzenediazonium Salt and Alkyl Iodides [15]

Heteroaromatic base	Alkyl iodide	Orientation %	Yield [a] %
Lepidine	*i*-Pr	2	93
"	*n*-Bu	2	98
"	*t*-Bu	2	76
"	c-C_6H_{11}	2	95
Quinaldine	*i*-Pr	4	96
"	c-C_6H_{11}	4	91
Quinoline	c-C_6H_{11}	2 (44), 4 (56)	93
Isoquinoline	c-C_6H_{11}	1	90

[a] Based on the converted base. Conversions 30-100%.

We have generally obtained good results, as Tables 3 and 4 illustrate; there are, however, some structural limitations. With aroyl peroxides, the reaction does not work with *t*-alkyl iodides because it does not lead to an aryl radical, due to competitive ionic reactions. A further general limitation occurs with substrates possessing activated C-H bonds or very electronrich unsaturated (olefinic or aromatic) systems; in these cases, iodine abstraction does not occur because the reactions of the aroyloxy radical, ArCOO·, initially formed, with the substrate (hydrogen abstration, addition to the unsaturated system) are faster than its decarboxylation [22] and aryl radicals are not formed. It is possible to overcome, in part, this limitation by increasing the reaction temperature, which affects the monomolecular decarboxylation of ArCOO· more than the intermolecular reactions of the same radical. The main limitation with diazonium salts is due to the high rate of addition of nucleophilic alkyl radicals to the diazonium group, which competes with the heterocyclic substitution leading to the free-radical diazocoupling reaction [23]. To overcome this competition it is necessary to keep the stationary concentration of the diazonium salt low during the reaction; this has been achieved by slow addition of the diazonium salt to a solution of protonated heteroaromatic base, alkyl iodide and reducing metal salt in DMSO. The fast reduction of the diazonium salt by the metal salt determines its low stationary concentration.

We have utilized the phenyl or the benzoyloxy radicals to generate alkyl radicals, useful for heteroaromatic substitution, also by hydrogen abstraction from C-H bonds [15]. In this case, synthetic limitations are more pronounced because the rates of hydrogen abstraction by phenyl radical (~ 10^6 $M^{-1}s^{-1}$) are of the same order of magnitude than the rates of addition to the heterocyclic ring (Table 1); moreover, the regio- and chemoselectivity of hydrogen abstraction is very low. Thus, in order to have good selectivity in the heteroaromatic alkylation, it is necessary to use simple molecules, which have no problems of selectivity (*i.e.* methanol, cycloalkanes, dioxane, trioxanes *etc.*) and can be practically used in large excess, easy to recover, in order to avoid addition of the phenyl radical to the heterocyclic ring. Good results have been also obtained with substrates in which a particular C-H bond is remarkably more reactive than the others (*i.e.* α C-H bonds in ethanol or THF).

The selectivity is still good when the hydrogen abstraction leads to only one kind of nucleophilic radical. Thus, in a mixture of solvents, such as cyclohexane, chloroform and acetonitrile, the cyclohexylation of the heteroaromatic base selectively takes place, even if the $\cdot CCl_3$ and $\cdot CH_2CN$ radicals are extensively formed; the electrophilic character of these radicals completely inhibits the reaction with the protonated heterocyclic ring. Similarly, ethyl acetate gives an electrophilic, $\cdot CH_2COOEt$, and a nucleophilic, MeCOOCHMe, radical, but only the latter reacts with the heterocyclic compound.

The stoichiometry of the reaction is shown by equations 18 and 19, referring respectively to hydrogen abstraction by the phenyl or the benzoyloxy radical. When the strength of the C-H bond is relatively low and its electron availability is high (*i.e.* the α C-H bonds in alcohols and ethers) the abstraction of hydrogen by the benzoyloxy radical is faster than its decarboxylation; in some cases, however, equations 18 and 19 simultaneously contribute to the overall process.

$$\text{Het-H} + \text{RH} + (\text{PhCOO})_2 \longrightarrow \text{Het-R} + \text{PhCOOH} + \text{Ph-H} + CO_2 \quad (18)$$

$$\text{Het-H} + \text{RH} + (\text{PhCOO})_2 \longrightarrow \text{Het-R} + 2\,\text{PhCOOH} \quad (19)$$

Some results are reported in Table 5.

The mechanism of the reaction is substantially similar to that of Scheme I; the only difference concerns the generation of the alkyl radical by hydrogen, instead of iodine, abstraction.

All the considerations concerning the use of aryl radicals for the homolytic alkylation of heteroaromatic bases suggested that more general, simple and cheap sources of alkyl radicals by iodine or hydrogen abstraction would have been of undoubted interest.

In pursuing this aim, we have developed a simple, cheap and general source of alkyl radicals, useful for aromatic substitution, from alkyl iodides by using DMSO as a mediator [23b,24]. Paradoxically, we have utilized a very reactive and unselective radical species, the hydroxyl radical, to develop highly selective syntheses also for complex molecules. The design of an effective chain process was based, once again, on the knowledge of rate constants of the steps involved in the chain, and of equilibrium constants of iodine abstraction from alkyl iodides by methyl radical.

Now the rate constants for most of the reactions of the hydroxyl radical with many organic and inorganic compounds (hydrogen abstraction, addition to unsaturated systems, oxidation *etc.*) stand in the range 10^7-10^{10} $M^{-1}s^{-1}$ and it could appear unwise to utilize this radical for selective syntheses; however, we have dominated the high reactivity and the low selectivity of the OH reactions by using DMSO as the solvent. The hydroxyl radical is easily obtained by the well-known redox decomposition of hydrogen peroxide by Fe(II) salts (equation 20) and reacts then very rapidly with DMSO [25] (equation 21) so that the possible fast, competitive and unselective reactions with other substrates, including alkyl iodides [26] (equation 22) utilized as sources of alkyl radicals, are minimized by the excess of solvent.

Table 5

Alkylation of Heteroaromatic Bases by Hydrogen Abstraction from RH by $(PhCOO)_2$ [15]

Heteroaromatic base	RH	Orientation	Conversion (%)	Yield (%)
Lepidine	c-C_6H_{12}	2	74	96
"	c-C_6H_{12}	2	100	86
"	MeOH	2	74	98
"	$MeCH_2OH$	2	38	87
"	DMF	2	57	83
"	dioxane	2	71	91
"	$MeCOOCH_2Me$	2	35	78
Quinaldine	c-C_6H_{12}	4	68	94
"	c-C_8H_{16}	4	65	98
"	THF	4	58	82
"	dioxane	4	65	87
Isoquinoline	c-C_6H_{12}	1	72	87
4-Cyanopyridine	c-C_6H_{12}	2 (67), 2,6 (33)	58	93
"	c-C_8H_{16}	2 (65), 2,6 (35)	60	96
"	dioxane	2 (72), 2,6 (28)	61	88
"	THF	2 (76), 2,6 (24)	58	85

$$H_2O_2 + Fe^{2+} \longrightarrow HO^{\cdot} + OH^{-} + Fe^{3+} \quad (20)$$

$$HO^{\cdot} + Me\text{-}SO\text{-}Me \longrightarrow \overset{HO}{\underset{Me}{\overset{\diagdown}{\diagup}}}\!\!>S\!<\!\!\overset{O^{\cdot}}{\underset{Me}{\overset{\diagdown}{\diagup}}} \quad k = 7 \times 10^9\ M^{-1}s^{-1} \quad (21)$$

$$RI + {}^{\cdot}OH \longrightarrow R\text{-}\dot{I}\text{-}OH \quad k > 10^9\ M^{-1}s^{-1} \quad (22)$$

The Radical adduct undergoes a fast β-fission, acting as a selective source of methyl radicals [25] (equation 23).

$$\overset{HO}{\underset{Me}{\overset{\diagdown}{\diagup}}}\!\!>S\!<\!\!\overset{O^{\cdot}}{\underset{Me}{\overset{\diagdown}{\diagup}}} \longrightarrow Me^{\cdot} + MeSO_2H \quad k = 1.5 \times 10^7\ M^{-1}s^{-1} \quad (23)$$

Now the methyl radical abstracts iodine from alkyl iodides according to the equilibrium of equation 24.

$$Me^{\cdot} + I\text{-}R \rightleftharpoons Me\text{-}I + R^{\cdot} \quad k > 10^6\ M^{-1}s^{-1} \quad (24)$$

The rate constants for iodine abstraction (equation 24) are generally higher than those for most of the other possible competitive reactions of the methyl radical, and equilibrium constants are strongly affected by the stability of the alkyl radical [27] (Table 6).

Following these kinetic and thermodynamic data we have developed a new effective general method for the substitution of protonated heteroaromatic bases, whose stoichiometry is shown by equation 25.

$$Het\text{-}H + RI + MeSOMe + H_2O_2 \longrightarrow Het\text{-}R + MeI + MeSO_2H + H_2O \quad (25)$$

Some results obtained with a variety of heteroaromatic bases and alkyl iodides are reported in Table 7. The reaction has also been successfully applied to complex molecules, such as the iodosugar [21] of equation 16.

Table 6

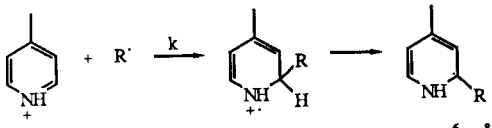
Equilibrium Constants for the Reaction

$$RI + Me^{\cdot} \rightleftharpoons R^{\cdot} + MeI$$

R	K
Et	20.1
i-Pr	468
t-Bu	$1.7\ 10^4$

A complex, but selective chain is involved in the reaction of equation 25; equations 20-24 are involved in the initial

steps of the chain. The knowledge of the rate constants for alkyl radical addition to protonated heteroaromatic bases (equation 26) and for the oxidation of the pyridinyl-type radical intermediate (equation 27) have contributed to fulfill the invention of effective redox chains.

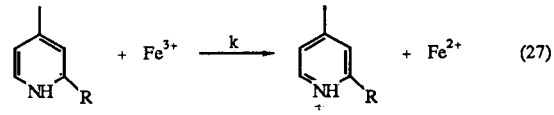


$k \sim 10^6$-10^8 $M^{-1}s^{-1}$ (26)

Table 7

Alkylation of Heteroaromatic Bases by Alkyl Iodide, Hydrogen Peroxide and DMSO [24]

Heteroaromatic compound	R	Orientation (%)	Conversion (%)	Yield (%)
Lepidine	*i*-Pr	2	90	88
"	*i*-bu	2	93	91
"	c-C_6H_{11}	2	88	92
"	*n*-Pr	2	75	82
"	*n*-Bu	2	73	78
"	*t*-Bu	2	98	86
Quinaldine	*i*-Pr	4	95	96
"	c-C_6H_{11}	4	94	97
"	*n*-Bu	4	72	81
Quinoline	*i*-Pr	2 (25), 4 (36) 2,4 (39)	97	94
"	*i*-Bu	2 (27), 4 (38) 2,4 (35)	95	92
"	*n*-Pr	2 (36), 4 (39) 2,4 (25)	78	82
"	*n*-Bu	2 (40), 4 (43) 2,4 (17)	75	77
"	*t*-Bu	2	96	87
Isoquinoline	*i*-Pr	1	86	88
"	c-C_6H_{11}	1	79	84
Acridine	*i*-Pr	9	78	92
"	c-C_6H_{11}	9	83	96
4-cyanopyridine	*i*-Pr	2 (67), 2,6 (33)	86	95
"	c-C_6H_{11}	2 (62), 2,6 (38)	92	93
"	*t*-Bu	2 (58), 2,6 (42)	96	94
4-acetylpyridine	*i*-Pr	2 (68), 2,6 (32)	85	95
4-methylpyridine	c-C_6H_{11}	2	35	99
Pyrazine	"	2	45	78
Quinoxaline	"	2 (68), 2,3 (32)	86	81
Benzothiazole	"	2	38	87



$k > 10^8$ $M^{-1}s^{-1}$ (27)

The fact that the equilibria of equation 24 are shifted at right is not in itself a sufficient condition for a high selectivity, because the reaction rates of Me· and R· radicals can be quite different. When the enthalpic factor governs the reactivity, as in iodine abstraction (equation 24), the methyl radical is more reactive than primary, secondary, tertiary and, in general, α-substituted alkyl radicals; this can counterbalance the unfavourable equilibria. The radical source (equation 24) becomes selective because the polar effects are dominant in the addition to the heterocyclic ring (equation 6). Thus the enthalpic factor governs the equilibria of equation 24, whereas the polar factor governs the addition of alkyl radicals to the heterocyclic ring (equations 6 and 26). Since primary, secondary and tertiary alkyl radicals without electronwithdrawing groups in α-position are more nucleophilic than the methyl radical [5], both factors work in the same direction, that is, the formation of R· radical is favoured in the equilibrium of equation 24 for enthalpic reasons, and it is more reactive than methyl radical towards heterocyclic compounds for polar reasons and a highly selective substitution occurs.

We have also utilized *t*-butyl hydroperoxide and di-*t*-butylperoxide as sources of methyl radical in the substitution of heteroaromatic bases by alkyl iodides [23b,28], according to the overall stoichiometry of equations 28 and 29.

Het-H + RI + *t*-BuOOH ⟶ Het-R + MeI + MeCOMe + H_2O (28)

Het-H + RI + $(t\text{-BuO})_2$ ⟶ Het-R + MeI + MeCOMe + *t*-BuOH (29)

Some results are shown in Tables 8 and 9.

Table 8

Alkylation of Heteroaromatic Bases by Alkyl Iodides and $(t\text{-BuO})_2$ [28]

Heteroaromatic base	Alkyl iodide	Orientation (%)	Conversion (%)	Yield (%)
Lepidine	$C_6H_{13}I$	2	85	87
Lepidine	2-$C_6H_{13}I$	2	100	85
Lepidine	c-$C_6H_{11}I$	2	100	89
Quinaldine	$C_6H_{13}I$	4	78	82
Quinaldine	2-$C_6H_{13}I$	4	95	86
Quinaldine	c-$C_6H_{11}I$	4	91	81
Isoquinoline	c-$C_6H_{11}I$	1	87	92
4-cyanopyridine	c-$C_6H_{11}I$	2 (45) 2,6 (5)	88	83
Quinoxaline	c-$C_6H_{11}I$	2	72	78
Benzothiazole	c-$C_6H_{11}I$	2	68	81

In both cases the methyl radical is formed by β-fission of the *t*-BuO radical (equation 30).

$$t\text{-BuO}^{\cdot} \xrightarrow{k_d} \text{MeCOMe} + \text{Me}^{\cdot} \qquad (30)$$

Table 9

Alkylation of Heteroaromatic Bases by Alkyl Iodides and *t*-BuOOOH [28]

Heteroaromatic base	Alkyl iodide	Orientation (%)	Conversion (%)	Yield (%)
Lepidine	BuI	2	86	84
Lepidine	*i*-PrI	2	96	94
Lepidine	c-C_6H_{11}I	2	92	93
Lepidine	*i*-BuI	2	95	93
Quinaldine	BuI	4	78	87
Quinaldine	*i*-PrI	4	70	92
Quinaldine [b]	*i*-PrI	4	100	91
Quinaldine	c-C_6H_{11}I	4	68	90
Quinoline	BuI	2 (30), 4 (32) 2,4 (38)	79	94
Quinoline	*i*-PrI	2 (25), 4 (27) 2,4 (48)	94	96
Isoquinoline	*i*-PrI	1	100	86
Isoquinoline	c-C_6H_{11}I	1	100	93
Acridine	*i*-PrI	9	85	90
4-Cyanopyridine		2 (71), 2,6 (29)	78	81
4-Cyanopyridine	c-C_6H_{11}I	2 (68), 2,6 (32)	74	83
4-Acetylpyridine	*i*-PrI	2 (65), 2,6 (35)	76	87
Quinoxaline	*i*-PrI	2 (53), 2,3 (47)	78	89
Quinoxaline	c-C_6H_{11}I	2 (62), 2,3 (38)	72	91
Benzothiazole	*i*-PrI	2	68	84
Benzothiazole	c-C_6H_{11}I	2	72	88

[a] Based on the converted base.
[b] The amount of *t*-BuOOH was doubled.

With *t*-BuOOH the *t*-BuO radical is obtained by redox decomposition with Fe(II) salt (equation 31).

$$t\text{-BuOOH} + \text{Fe}^{2+} \longrightarrow t\text{-BuO}^{\cdot} + \text{Fe}^{3+} + \text{OH}^{-} \qquad (31)$$

The methyl radical formed in equation 30 abstracts iodine from the alkyl iodide according to the equilibrium of equation 24 and the alkyl radical selectively attacks the heterocyclic ring, generating an effective redox chain (equations 26 and 27). To make equation 30 effective, it is necessary to minimize the two main competitive reactions of *t*-BuO radical, which are hydrogen abstraction from C-H bonds in the reacting system (equation 32) and reduction by Fe(II) salt (equation 33).

$$t\text{-BuO}^{\cdot} + \text{RH} \xrightarrow{k_a} t\text{-BuOH} + \text{R}^{\cdot} \qquad (32)$$

$$t\text{-BuO}^{\cdot} + \text{Fe}^{2+} + \text{H}^{+} \longrightarrow t\text{-BuOH} + \text{Fe}^{3+} \qquad (33)$$

To minimize equation 32 we have taken advantage of solvent and temperature effects; the influence of solvent and temperature on the competition between hydrogen abstraction (k_a) and decomposition (k_d) of *t*-BuO$^{\cdot}$ is known since many years [29]. The rate of decomposition has been evaluated 10^3 s^{-1} at room temperature in the gas phase [30], whereas in aqueous solution a value > $10^6 s^{-1}$ has been reported [31]. Some data concerning hydrogen abstraction from cyclohexane are reported in Table 10; these data suggested that refluxing in acetic acid should be particularly effective because, in addition to solvent and temperature effects, hydrogen abstraction from acetic acid is a relatively low process for polar reasons. To minimize equation 33 it was important to keep the stationary concentration of the Fe(II) salt low in the reacting sytem; this was obtained by using small amounts of Fe(III) acetate as catalyst. Since no reaction occurs, under the same conditions, in the absence of Fe(III) salt, the initiation of the redox chain seems to be due to equation 34, whereas the initiation by thermal decomposition of hydroperoxide seems irrelevant in refluxing acetic acid.

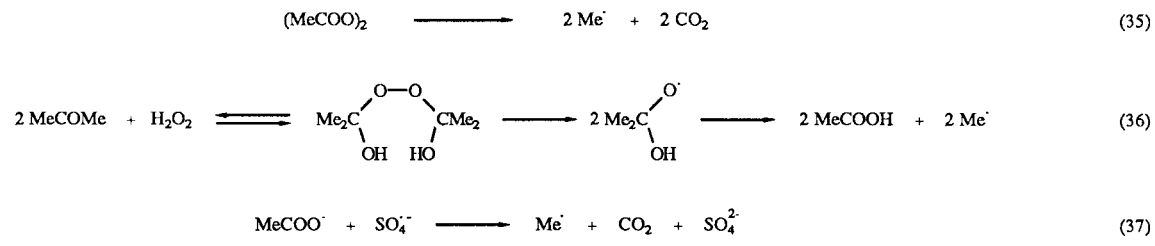
$$t\text{-BuOOH} + \text{Fe}^{3+} \rightleftharpoons t\text{-BuOO}^{\cdot} + \text{Fe}^{2+} + \text{H}^{+} \qquad (34)$$

Table 10

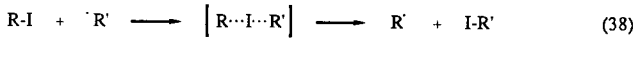
Temperature and Solvent Effects on k_a/k_d [29] (hydrogen abstraction from cyclohexane)

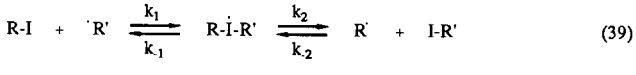
T°	100	70	40	25	0
CCl_4	4.14	11.1	39.9	87.8	293
benzene	2.82	7.62	24.7	48.6	207
MeCOOH	< 1	1.34	2.9	4.87	12.6

Reaction 34 is much slower than reactions 31 and 33, so that the steady state concentration of Fe(II) salt remains very low during the reaction. Other oxidative sources of methyl radical proved to be successful for this general process of homolytic alkylation of heteroaromatic bases [21]: decomposition of acetyl peroxide (equation 35), thermal decomposition of hydrogen peroxide in acetone (equation 36), oxidative decarboxylation of acetic acid by persulphate (equation 37).



A question arises concerning this general source of alkyl radicals, which is why a small difference in the energies of C-I bonds (56.5 Kcal/mol for MeI and 52.4 Kcal/mol for *t*-BuI) determines such a high selectivity in iodine abstraction; the fact is striking if we compare iodine abstraction to hydrogen abstraction from C-H bonds, in which larger differences in C-H bond energies are reflected in a lower selectivity. Under complete thermodynamic control, this behaviour would be explained by the fact that small variations in bond strength are completely exploited. However, for processes under kinetic control thermochemistry will only be partially reflected in transition states, as shown by the Evans-Polanyi ($E_a = \alpha \Delta H° + C$) and similar relationships. A reasonable explanation is that thermochemisry is reflected in the transition state of iodine abstraction more than in the transition state of hydrogen abstraction. An alternative explanation is that the mechanism of iodine abstraction is not that of the classical atom-transfer process (equation 38), but an addition-elimination process (equation 39).





Equation 22 is circumstantial evidence for a possible addition-elimination mechanism, even if it can be hazardous to extrapolate the behaviour of hydroxyl radical to carbon-centered radicals. A personal communication by K. U. Ingold, however, would suggest that some spectroscopic behaviour concerning methyl iodide could be related to an intermediate radical adduct, Me-I-Me, as indicated by equation 39, but this is a preliminary observation, which needs a thorough examination.

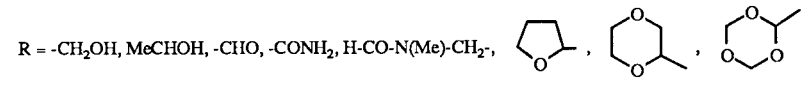
When the rate of iodine abstraction is on diffusion controlled range, as with aryl radicals (equation 11), it makes less sense to distinguish between the mechanisms of equations 38 and 39, because the fast addition of the aryl radical to iodine must be substantially simultaneous to the breaking of the C-I bond in the alkyl iodide. When R' is a methyl, or in general an alkyl radical, the overall iodine transfer rate is lower and it may result from the kinetic constants involved in the equilibrium of equation 39; the selectivity would be determined by homolysis of the C-I bonds of the intermediate radical adduct R-I-R'.

We have developed sources of alkyl and carbonyl radicals, useful for heteroaromatic substitution, by hydrogen abstraction with oxygen- and nitrogen-centered radicals; some of these processes are also suitable for practical applications [32] because of the general character, the high yields and selectivities, the cheap reagents and catalysts, the simple experimental conditions and the interest of the reaction products.

Important substitution reactions, such as hydroxymethylation [33], α-hydroxyethylation [34], formylation [35], carbamoylation [34], dioxanilation [33], α-tetrahydrofuranylation [34], α-*N*-amidoalkylation and acylation [33] have been developed under catalytic conditions by very trivial reagents, such as methanol, ethanol, formaldehyde, formamide, dioxane, THF, DMF, *N*-methylacetamide, aldehydes according to the general equations **40** and **41**.

All these reagents have little problems of regioselectivity, are quite inexpensive and can be used in large excess as solvents, thus minimizing the low chemoselectivity of hydrogen abstraction. Some results are reported in Tables 11 and 12.

With hydrogen peroxide or *t*-BuOOH alkyl radicals are generated by hydrogen abstraction according to equations 42 and 43.



R' = H or *t*-Bu R" = H or SO_3H

Table 11

Catalytic Substitution of Heteroaromatic Bases

$$\text{Het-H} + \text{R-H} + \text{R'OOH} \longrightarrow \text{Het-R} + \text{R'OH} + H_2O$$

Het-H	R-H	R'OOH	Orientation	Yield % [a]
Quinoline	$HCONH_2$	HOOH	2,4-Disubstituted	97
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
Quinaldine	"	"	4	94
Isoquinoline	"	"	1	92
Quinoxaline	"	"	2	94
Benzothiazole	"	"	2	90
Lepidine	"	"	2	94
"	"	HOOH	2	93
"	Dioxane	"	2	90
"	"	*t*-BuOOH	2	95
"	Methanol	"	2	99
"	"	HOOH	2	95
"	Benzaldehyde	*t*-BuOOH	2	75
Acridine	"	"	9	70
2-Cyanoquinoline	"	"	4	75

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

$$\text{R'OOH} + Fe^{2+} \longrightarrow \text{R'O}^{\cdot} + Fe^{3+} + OH^{-} \quad (42)$$

$$\text{R'O}^{\cdot} + \text{H-R} \longrightarrow \text{R'OH} + \text{R}^{\cdot} \quad (43)$$

With hydroxylamine or hydroxylamine-*O*-sulphonic acid alkyl radicals are generated according to equations 44-46.

$$\overset{+}{N}H_3OH + Ti^{3+} \longrightarrow \overset{+}{N}H_3^{\cdot} + Ti^{4+} + OH^{-} \quad (44)$$

$$\overset{+}{N}H_3OSO_3^{-} + Fe^{2+} \longrightarrow \overset{+}{N}H_3^{\cdot} + Fe^{3+} + SO_4^{-} \quad (45)$$

$$RH + \overset{+}{N}H_3^{\cdot} \longrightarrow R^{\cdot} + NH_4^{+} \quad (46)$$

The mechanism of the reactions 40 and 41 is substantially identical to that described for iodine abstraction; the process is catalytic in the metal salt and the only difference is the source of carbon-centered radical. The iodine transfer process has a much more general character, due to the high selectivity of io-dine abstraction, and can be also applied to complex sub-strates. The hydrogen transfer process has more limited appli-cations, which, however, concern some fundamental reactions of organic chemistry, as those shown by equations 40 and 41, particularly useful for their potential practical use.

Carboxylic Acids as a Source of Alkyl Radicals.

The oxidative decarboxylation of carboxylic acids is a quite

Table 12

Catalytic Substitution of Heteroaromatic Bases

$$\text{Het-H} + \text{RH} + \text{NH}_2\text{OR''} \longrightarrow \text{Het-R} + \text{NH}_3 + \text{R''OH}$$

Het-H	RH	R''	Orientation	Conversion (%)	Yield %
Lepidine	MeOH	H	2	95	82
"	EtOH	H	2	91	70
"	dioxane	H	2	97	83
"	THF	H	2	69	67
"	DMF	H	2	56	61
"	MeOH	OSO_3H	2	85	93
"	dioxane	"	2	93	96
"	THF	"	2	25	96
"	$HCONH_2$	"	2	50	84
"	DMF	"	2	70	80
Quinaldine	MeOH	"	4	70	97
4-cyanopyridine	MeOH	"	2	36	78

general route to alkyl radicals, useful for aromatic substitution (equation 47).

$$\text{RCOOH} \xrightarrow{-e} \text{R}^{\cdot} + \text{CO}_2 + \text{H}^{+} \qquad (47)$$

A variety of chemical or electrochemical oxidations have been utilized. The method of choice is generally the silver-catalyzed decarboxylation by persulphate because of the simplicity, the general character, the low price of the oxidant and the high yields and selectivity [3,36].

We have recently developed a new simple and general procedure [37], based on the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate; the method can be useful in those cases in which reagents have particular problems of solubility or a pronounced sensitivity to other oxidants. The stoichiometry of the reaction is shown by equation 48.

$$\text{Het-H} + \text{RCOOH} + \text{PhI(OAc)}_2 \xrightarrow{h\nu}$$

$$\text{Het-R} + \text{PhI} + 2\,\text{AcOH} + \text{CO}_2 \qquad (48)$$

Since iodosoacetate is easily prepared from iodobenzene, acetic anhydride and hydrogen peroxide (equation 49), the iodobenzene, generated in the reaction, can be recovered and recycled for synthesis on a large scale.

$$\text{PhI} + 2\,\text{Ac}_2\text{O} + \text{H}_2\text{O}_2 \longrightarrow \text{PhI(OAc)}_2 + 2\,\text{AcOH} \qquad (49)$$

The reaction mechanism is illustrated by Scheme III.

The high reducing character of the pyridinyl-type radical accounts for the induced decomposition of iodosocarboxylate in a chain process. Some results are reported in Table 13.

The relative rates reported in Table 14 among acetic acid, primary, secondary and tertiary carboxylic acids, obtained in competitive experiments, indicate that the selectivity is high between methyl and other alkyl radicals, whereas it is lower among primary, secondary and tertiary alkyl radicals. These relative rates well explain the selective use of iodosobenzene diacetate for the alkylation of heteroaromatic bases by carboxylic acids, even if the quantitative meaning of these data is affected by the fact that we do not know the equilibria between iodosobenzene diacetate and carboxylic acids under the reaction conditions.

Selectivity in Monosubstitution of Acylation and Alkylation of Heteroaromatic Bases by Carboxylic Acids.

Scheme III

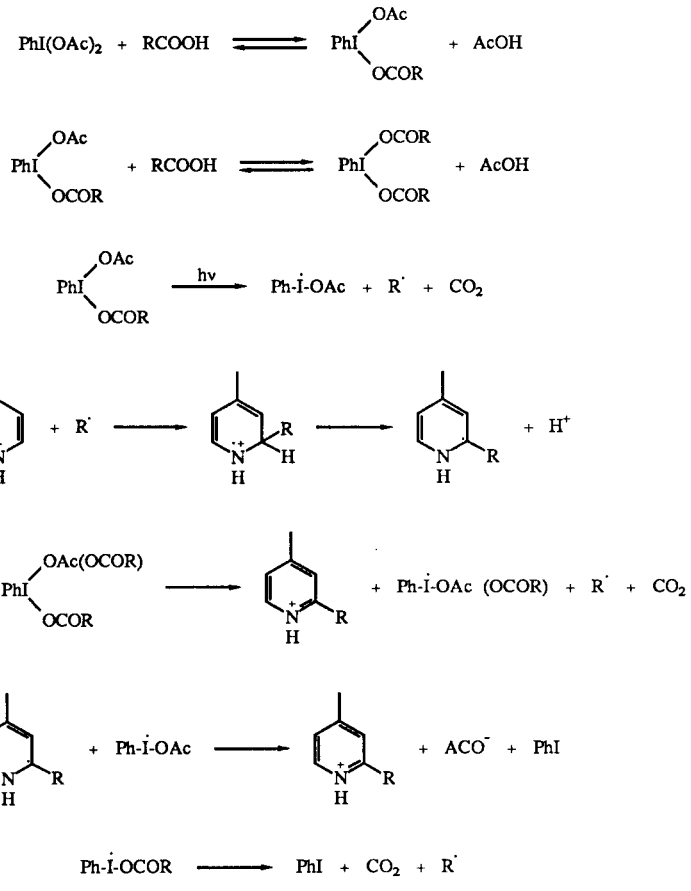


Table 13

Alkylation of Heteroaromatic Bases by Carboxylic Acids and Iodosobenzene Diacetate

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

[a] Conversion of the starting base. [b] Yields based on the converted base.

Table 14

Competitive Experiments in the Alkylationof Lepidine

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

The substitution of protonated heteroaromatic bases by nucleophilic alkyl and acyl radicals reflects the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity; the synthetic advantage and disadvantages are, therefore, opposite. Thus, in the electrophilic process acylation is much more selective than 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, thus favouring polysubstitution. In the homolytic process, the behaviour is opposite, due to the opposite polar character of the reacting species: carbonyl groups activate [38] and alkyl groups deactivate [39] the heterocyclic ring. Consequently, when more positions of high nucleophilic reactivity are available in the heterocyclic ring (α and γ) polysubstitution by carbonyl radicals easily occurs, and it is difficult to arrest the reaction to monosubstitution. On the other hand, alkyl groups are poor polar substituents compared with acyl groups and the degree of deactivation is not sufficient to arrest the reaction to monosubstitution at high conversions of the substrates, so that the problem of polysubstitution is important also in homolytic alkylation. These limitations are much less severe as compared with electrophilic alkylation, because in any case only the α and γ positions of the protonated ring are generally attacked by alkyl and acyl radicals and, when only one of these positions is free, only monosubstitution is easily obtained in high yields at complete conversions (that is, a carbonyl group is much less activating than the protonated heterocyclic nitrogen).

Acylation.

The monosubstitution by carbonyl radicals is of synthetic interest in many cases, in which more free reactive positions in the heterocyclic ring are available.

Years ago we [34,40] managed to partially overcome the problem by taking advantage of the fact that carbonyl-substituted derivatives are always less basic than the starting bases and by consequently adjusting the medium acidity in order that the starting base is, at least in part, protonated while the monosubstituted derivative is unprotonated; the protonated species is much more reactive and monosubstitution can be effected with reasonable selectivity.

A further improvement has been obtained by taking advantage of the increased lipophilicity [41], in addition to the decreased basicity, of the substituted heterocyclic compound, and working in a two-phase system (water and a suitable solvent). Good results have been obtained by simply modifying the method that we had previously developed [42] for the alkoxycarbonylation of heteroaromatic bases in aqueous solution, in which both the source of alkoxycarbonyl radical, $^{\cdot}$COOR, and the protonated heterocyclic compound are sufficiently soluble (equation 50). The alkoxycarbonyl radical was generated by redox decomposition of the pyruvic ester peroxide [42] (equation 51).

The simple, but effective, change involves the use of a solvent insoluble in water, which continuously extracts the less basic and more lipophilic monosubstitution product, preventing from polysubstitution. We also developed a quite general method for the acylation of heteroaromatic compounds from aldehydes and *t*-BuOOH [40,43] (equation 52).

Acyl radicals were generated according to equations 53 and 54, which initiate a redox chain [43].

$$t\text{-BuOOH} + Fe^{2+} \longrightarrow t\text{-BuO}^{\cdot} + OH^{-} + Fe^{3+} \qquad (53)$$

$$t\text{-BuO}^{\cdot} + RCHO \longrightarrow t\text{-BuOH} + RCO^{\cdot} \qquad (54)$$

Attempts [44] to modify the general reaction of equation 52 in order to increase the selectivity of monoacylation by a two-phase system failed or gave poor results because generally the organic solvent completely extracts aldehydes from the aqueous solution, thus preventing from the generation of acyl radicals; only lower aliphatic aldehydes (acetaldehyde, propionaldehyde), which have some solubility in water, gave a moderate improvement in monoacylation. We have, therefore, utilized a different source of acyl radicals, which has a quite general character and has allowed us to develop a two-phase system particularly suitable for monoacylation. It is based on the silver-catalyzed decarboxylation of α-ketoacids by persulphate. We had already extensively utilized this procedure for the homolytic alkylation of heteroaromatic bases by carboxylic acids [39,45]; the generation of acyl radicals from α-ketoacids according to equations 55-57 is easier than that of alkyl radicals from the corresponding carboxylic acids and requires milder conditions.

$$\text{Het-H} + \text{MeCOCOOR} + H_2O_2 \longrightarrow \text{Het-COOR} + \text{MeCOOH} + H_2O \qquad (50)$$

$$\text{Me-C(HO,OOH)-COOR} + Fe^{2+} \longrightarrow Fe^{3+} + OH^{-} + \text{Me-C(HO,O}^{\cdot}\text{)-COOR} \longrightarrow \text{MeCOOH} + {}^{\cdot}\text{COOR} \qquad (51)$$

$$\text{Het-H} + \text{RCHO} + t\text{-BuOOH} \longrightarrow \text{Het-COR} + t\text{-BuOH} + H_2O \qquad (52)$$

$$S_2O_8 + Ag^+ \longrightarrow SO_4^{\cdot} + SO_4^{2-} + Ag^{2+} \quad (55)$$

$$SO_4^{\cdot} + Ag^+ \longrightarrow SO_4^{2-} + Ag^{2+} \quad (56)$$

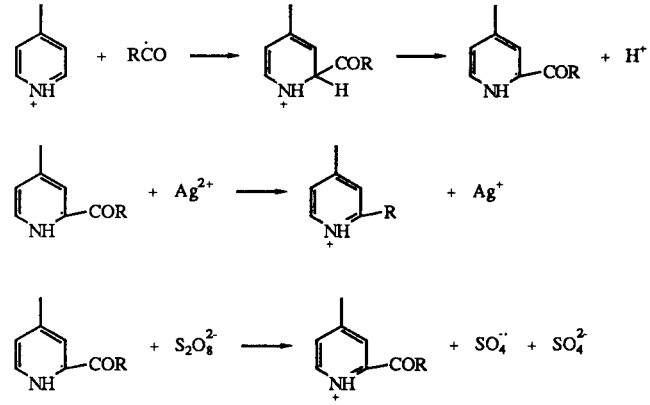
$$R\text{-}CO\text{-}COOH + Ag^{2+} \longrightarrow R\dot{C}O + CO_2 + H^+ + Ag^+ \quad (57)$$

The reaction (equation 58) takes place in aqueous solution at moderate temperature (20°-40°C) and both aromatic and aliphatic α-ketoacids are in general sufficiently water-soluble to allow an effective oxidation also in a two-phase system. On the other hand, reaction 57 is particularly selective: a very low concentration of α-ketoacid in aqueous solution is sufficient to give a selective oxidation.

$$Het\text{-}H + R\text{-}CO\text{-}COOH + S_2O_8^{2-} \longrightarrow Het\text{-}COR + CO_2 + 2\,HSO_4^- \quad (58)$$

The acylation takes place according to the chain process (Scheme IV), which has a general character for the substitution of heteroaromatic bases by nucleophilic carbon-centered radicals.

Scheme IV



The results of Tables 15 and 16 indicate that several factors are important in determining the selectivity of monoacylation:

i) The less basic that the heterocyclic compound is, the easier is the monosubstitution, because the introduction of an acyl group further decreases basicity and makes the extraction by the organic solvent easier in non strongly acidic medium. Thus, it is relatively more difficult to obtain monosubstitution with quinoline, which is the most basic among the investigated substrates (Tables 15 and 16).

Table 15

Acylation of 4-Cyanopyridine, 4-Acetylpyridine and Pyrazine by RCOCOOH

Heterocyclic compound	Solvent	Conversion (%)	R	Monoacyl (%)	Diacyl (%)
4-cyanopyridine	H_2O	52	Me	75	25
"	CH_2Cl_2/H_2O	59	Me	100	–
"	H_2O	100	Pr	28	72
"	CH_2Cl_2/H_2O	100	Pr	86	14
"	"	100	Ph	100	–
4-acetylpyridine	H_2O	30	Me	73	27
"	CH_2Cl_2/H_2O	75	Me	84	16
"	H_2O	100	Pr	14	86
"	CH_2Cl_2/H_2O	80	Pr	93	7
"	"	100	Ph	100	–
pyrazine	"	54	Me	100	–
"	H_2O	100	Pr	66	34
"	H_2O	100	Pr	–	100
"	CH_2Cl_2/H_2O	100	Pr	74	26
"	"	100	Ph	100	–

Table 16

Acylation of Quinoline and Quinoxaline by RCOCOOH

Heterocyclic compound	Solvent	Conversion (%)	R	Monoacyl (%)	Diacyl (%)
Quinoline	H_2O	66	Me	41	59
"	CH_2Cl_2/H_2O	74	Me	74	26
"	"	61	Et	90	10
"	H_2O	62	Pr	35	65
"	CH_2Cl_2/H_2O	83	Pr	84	13
"	"	100	Ph	100	–
Quinoxaline	"	63	Me	94	6
"	"	75	Pr	93	7
"	H_2O	74	Pr	42	58
"	CH_2Cl_2/H_2O	100	Ph	100	–

ii) To favour monosubstitution, the acidity of the medium must be the lowest compatible with protonation, at least in part, of the starting heteroaromatic base, in order to make the extraction of the unprotonated acylation product easier by the organic solvent.

iii) The higher the lipophilicity of the heteroaromatic base is and also of the acyl derivatives, the easier is the monosubstitution; thus the selectivity is higher with quinoxaline than with pyrazine and it increases in the series acetyl < propionyl < butyryl < benzoyl: with the benzoyl radical, the selectivity is excellent in all cases.

iv) The amounts of persulphate and α-ketoacids utilized influences the ratio between mono- and polyacylation: a large escess of reagents obviously favours polysubstitution. It is not possible to foresee the most suitable amount of persulphate necessary to obtain a given conversion, because the oxidation of the acyl radical (equations 59 and 60) is the main side reaction in competition with heteroaromatic acylation.

$$\dot{R}CO + S_2O_8^{2-} \longrightarrow SO_4^{\cdot-} + SO_4^{2-} + RCO^+ \xrightarrow{H_2O} RCOOH \quad (59)$$

$$\dot{R}CO + Ag^{2+} \longrightarrow Ag^+ + RCO^+ \xrightarrow{H_2O} RCOOH \quad (60)$$

The incidence of these side reactions is difficult to be foreseen because the addition of acyl radical to heteroaromatic bases is a reversible process (isotopic effect [15] and negative activation energy [46]), whereas reactions 59 and 60 are irreversible. Moreover the rates of addition of acyl radicals to the heterocyclic ring can significantly change with the substrate structure (*i.e.* the 2-position of 4-cyanoquinoline is about 130 times more reactive than the same position in 4-methylquinoline) [38]. The suitable amount of persulphate must therefore be experimentally determined in relation to a given conversion for each heteroaromatic base.

The simple and mild experimental conditions, the availability of a large variety of aliphatic and aromatic α-ketoacids, the high yields, the possibility to obtain mono- or polyacylation with good selectivity depending on the reaction conditions contribute to make this method particularly useful from a synthetic point of view. This must then be considered the method of choice for homolytic acylation of heteroaromatic bases.

Alkylation.

The introduction of an alkyl group deactivates the heterocyclic ring towards further alkylation; however, the polar effect of alkyl groups is generally poor. As the data of Table 17 indicates, an alkyl group always deactivates the heterocyclic ring and the degree of deactivation increases with the nucleophilic character of the attacking radical (Me < primary < secondary < tertiary alkyl). The data of Table 17, determined by the competitive method, have only a qualitative meaning and do not reflect relative rates, because the addition of alkyl radicals to the heterocyclic ring is reversible, especially with secondary and tertiary alkyl radicals, as shown by the isotopic effect [15].

Table 17

Relative Rates in Alkylation of the α-Position of Heteroaromatic Bases

Radical	4-Me-pyridine: Pyridine	Lepidine: Quinoline	2-c-Hex-4-CN-pyridine: 4-CN-pyridine
Me	0.53	–	–
n-Bu	0.32	0.70	0.33
i-Bu	0.28	0.60	0.20
t-Bu	0.15	0.16	< 0.10

Table 18

Alkylation of Quinoline and Quinoxaline with RCOOH and S_2O_8

Substrate	R	Conversion (%)	Solvent	Monoalkyl (%)	Dialkyl (%)
Quinoline	*n*-Bu	38	H_2O	100	–
"	*n*-Bu	87	H_2O	67	33
"	*n*-Bu	31	$PhCl/H_2O$	100	–
"	*n*-Bu	63	$PhCl/H_2O$	100	–
"	*i*-Bu	64	H_2O	86	14
"	*i*-Bu	100	H_2O	43	57
"	*i*-Bu	56	$PhCl/H_2O$	100	–
"	*i*-Bu	100	$PhCl/H_2O$	82	18
"	*t*-Bu	60	H_2O	100	–
"	*t*-Bu	54	$PhCl/H_2O$	100	–
Quinoxaline	*n*-Bu	8	H_2O	100	–
"	*n*-Bu	100	$PhCl/H_2O$	84	16
"	*i*-Bu	65	H_2O	85	15
"	*i*-Bu	100	$PhCl/H_2O$	52	48
"	*i*-Bu	87	$PhCl/H_2O$	91	8
"	*t*-Bu	90	H_2O	> 90	–
"	*t*-Bu	100	$PhCl/H_2O$	> 90	–

We considered the possibility to improve the selectivity of monoalkylation, always by using a two-phase system, because the introduction of an alkyl group generally increases the lipophilicity of heteroaromatic bases, even if the basicity is affected only to a small extent.

Among the numerous sources of alkyl radicals, which we have developed for heteroaromatic substitutions, the silver-catalyzed decarboxylation of carboxylic acids by persulphate once again proved to be the most suitable (equation 61).

$$\text{Het-H} + \text{RCOOH} + S_2O_8^{2-} \xrightarrow{Ag^+} \text{Het-R} + CO_2 + 2\,HSO_4^- \quad (61)$$

The reaction is characterized by high yields, inexpensive reagents, simple experimental conditions and can be easily carried out in aqueous solution: a small solubility of the carboxylic acid in water is sufficient for the reaction to proceed effectively.

The results of Tables 18 and 19 show that the two-phase system offers a twofold considerable advantage: it allows a considerable increase of the selectivity for monosubstitution and, at the same time, it significantly increases the synthetic potentiality. This is due to the fact that, in acidic aqueous medium, the decarboxylation of carboxylic acids by persulphate generally does not occur in the absence of silver salt. Besides, the silver catalysis is deactivated in aqueous solution by heterocyclic derivatives bearing two heteroatoms in the ring, such as diazines, thiazoles, imidazoles which complex the silver salt thus reducing its catalytic activity. The degree of deactivation is strictly connected with the rate of decarboxylation, which is related to the stability of the generated carbon-centered radical. Thus, the deactivation is moderate with α-keto- (Tables 15 and 16) and tertiary carboxylic acids, while it increases with secondary and it is almost complete with primary carboxylic acids.

Several years ago we have tried to overcome this difficulty by using an aqueous solution of carboxylic acid and sodium carboxylate [47]. Decarboxylation occurs in the absence of silver salt according to equations 62 and 63.

$$S_2O_8^{2-} \longrightarrow 2SO_4^{\cdot-} \quad (62)$$

$$RCOO^- + SO_4^{\cdot-} \longrightarrow R^{\cdot} + CO_2 + SO_4^{2-} \quad (63)$$

This method, however, is much less useful compared with the silver-catalyzed process mainly for two reasons: reaction of equation 63 is much less selective than reaction of equation 64, so that the presence of relatively high concentrations of carboxylate is necessary in order to obtain good results, whereas with silver catalysis low concentrations of carboxylic acids in acidic aqueous solution give excellent results.

Table 19

Alkylation of 4-Cyanopyridine and Pyrazine with RCOOH and S_2O_8

Substrate	R	Conversion (%)	Solvent	Monoalkyl (%)	Dialkyl (%)
4-cyanopyridine	*n*-Bu	97	H_2O	30	70
"	*n*-Bu	93	$PhCl/H_2O$	65	35
"	*i*-Bu	83	H_2O	67	33
"	*i*-Bu	90	$PhCl/H_2O$	87	13
"	*t*-Bu	100	H_2O	23	77
"	*t*-Bu	100	$PhCl/H_2O$	77	23
Pyrazine	*n*-Bu	45	H_2O	62	38
"	*n*-Bu	65	$PhCl/H_2O$	100	-
"	*i*-Bu	65	H_2O	51	49
"	*i*-Bu	100	$PhCl/H_2O$	86	14
"	*t*-Bu	90	H_2O	40	60
"	*t*-Bu	100	$PhCl/H_2O$	90	10

$$RCOOH + Ag^{2+} \longrightarrow R + CO_2 + H^+ + Ag^+ \quad (64)$$

Moreover, the low acidity in the absence of the silver salt strongly reduces protonation, reactivity and selectivity of weak bases, such as diazines, imidazoles, thiazoles. Now the two-phase system allows to overcome all these problems and makes the silver-catalyzed decarboxylation of carboxylic acids very effective also in the presence of heterocyclic derivatives bearing more than one heteroatom. Thus, under similar conditions and utilizing an excess of persulphate, the conversion of quinoxaline is in all cases complete with a two-phase system, but it is less than 10% with primary and 65% with secondary carboxylic acids.

The explanation of this behaviour can be related to the fact that the organic solvent extracts small amounts of unprotonated heteroaromatic bases, thus preventing from complexation of the silver salt in aqueous solution and therefore from deactivation of the metal salt catalysis.

The same factors, discussed for acylation, are also important for monoalkylation [48]. The basicity of the heteroaromatic compound, the acidity of the medium, the lipophilicity of the starting substrate and of the alkylated product, the conversions strictly connected with the amount of persulphate. The steric effect can also be important in alkylation; this is the case of quinoxaline, in which positions 2 and 3 are particularly reactive towards nucleophilic radicals. The introduction of an alkyl group in position 2 reduces the reactivity of position 3 not only for polar reasons, but also for steric reasons; the effect increases with the bulk of the alkyl group.

Compared with monoacylation, in which the key role is played by the decreased basicity and increased lipophilicity of the acylated product, the monoalkylation is favoured by the combination of polar deactivation and increased lipophilicity of the alkylated product.

The two-phase system is, therefore, a general, considerable improvement of the substitution of heteroaromatic bases with nucleophilic radicals and it contributes to make this reaction one of the most important for this class of heteroaromatic compounds.

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