

New General Processes of Homolytic Alkylation of Heteroaromatic Bases by t-BuOOH or (t-BuO)₂ and Alkyl Iodides[‡]

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New general, selective processes of homolytic alkylation of protonated heteroaromatic bases have been developed using alkyl iodides and t-BuOOH or (t-BuO)₂ as sources of alkyl radicals. Both processes are based on the generation of methyl radical from the peroxides, and on iodine abstraction from the alkyl iodide by the methyl radical.

The selective processes are the result of combined enthalpic and polar effects. The enthalpic factor governs the equilibrium of iodine abstraction, whereas the polar effect governs the reactivity of the alkyl radicals with the protonated heteroaromatic ring. A redox chain is operative with t-BuOOH and an unusual free-radical chain process is involved with (t-BuO)₂. Both chains are particularly effective because of the electron-transfer oxidation of the pyridinyl radical intermediate, the ionization potential of which (5.4–6.0 eV) is close to that of lithium (5.39 eV) or sodium (5.14 eV).

The homolytic alkylation and carbonylation (acyl, alkoxy-carbonyl, carbamoyl) of protonated heteroaromatic bases has been developed as one of the most important general reactions of this fundamental class of aromatic compounds. The interest is related to the high reactivity and selectivity of the nucleophilic alkyl and carbonyl radicals towards the protonated heterocyclic ring, determined by polar effects,^{1–4} and the fast and selective rearomatization of the heteroaromatic radical adduct, determined by effective redox chains.⁵ Thus, the availability of new general, simple and cheap sources of carbon-centered radicals useful for this purpose is of undoubted interest.

In pursuing this aim we have utilized alkyl iodides as sources of alkyl radicals. In this paper we describe new procedures obtained with alkyl iodides and t-BuOOH or (t-BuO)₂; these synthetic approaches have been, in part, briefly mentioned in a preliminary report.⁶

Results and discussion

The synthetic improvement is the result of combined enthalpic and polar factors. A key step is the fact that small differences in the strength of the C–I bonds are reflected in large variations of rates and equilibria of the iodine abstraction from alkyl iodides by carbon-centered radicals. Since the methyl radical is the least stable of the alkyl radicals, and since the strength of the C–I bond ranges from 56.5 kcal mol⁻¹ for CH₃I to 52.1 kcal mol⁻¹ for t-BuI,⁷ it is

possible to generate any kind of alkyl radical according to the equilibrium given in eqn. (1) (Table 1). The chemo-



selectivity of eqn. (1) is high, due to the fact that other possible competitive reactions of the methyl radical (hydrogen abstraction, addition to olefins or homocyclic aromatics etc.) are two or three orders of magnitude slower.⁸ However, the fact that the equilibrium of eqn. (1) is shifted to the right is not, in itself, sufficient to obtain a high selectivity, because the reaction rates of Me and R radicals with other substrates can be quite different. When the enthalpic factor governs the reactivity of the alkyl radicals, as for reaction (1), the methyl radical is more reactive than primary, secondary, tertiary and, in general, α -substituted alkyl radicals; this can counterbalance the unfavourable equilibrium.

The radical source becomes selective when polar effects are important. Then the addition rate of alkyl radicals to protonated heteroaromatic bases is strongly affected by their nucleophilic character, and all the primary, secondary and tertiary alkyl radicals without electron-withdrawing

Table 1. Equilibrium constants *K* for eqn. (1).

R	<i>K</i>
Et	20.1
i-Pr	468
t-Bu	17 × 10 ⁴

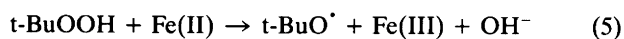
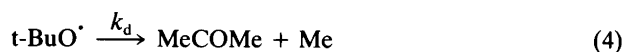
[‡] In part presented by F. Minisci as a main section lecture at the 32nd IUPAC congress in Stockholm, Sweden, August 2–7, 1989.

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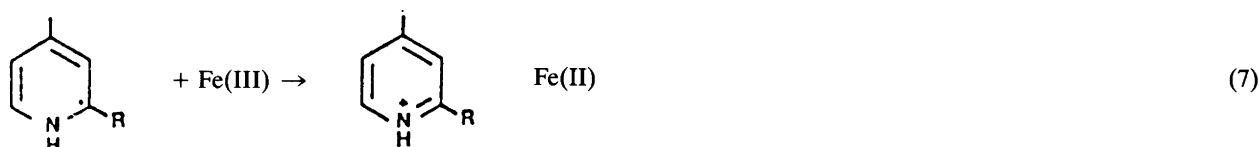
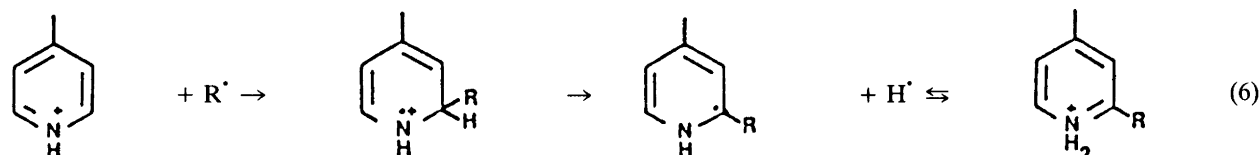


groups in the α -position are more nucleophilic than the methyl radical. Thus, both the favourable equilibrium, governed by the enthalpic effect, and the faster addition of the more nucleophilic radical to the heterocyclic ring, due to the polar effect, contribute to make the heteroaromatic substitution particularly selective; the methyl radical is not substantially involved in the attack at the heterocyclic ring.

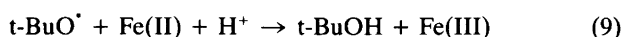
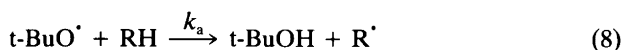
t-Butyl hydroperoxide and di-*t*-butyl peroxide were utilized as sources of the methyl radical in the substitution of the heteroaromatic base by alkyl iodides according to the overall stoichiometry of eqns. (2) and (3). In both cases, the methyl radical is formed by β -scission of the *t*-BuO radical [eqn. (4)]. With *t*-BuOOH, the alkoxy radical is obtained by redox decomposition with an Fe(II) salt [eqn. (5)].



The methyl radical formed in eqn. (4) abstracts iodine from the alkyl iodide according to the equilibrium of eqn. (1) and the alkyl radical selectively attacks the heterocyclic ring generating an effective redox chain [eqns. (6) and (7)]; the Fe(II) salt consumed in eqn. (5) is regenerated in eqn. (7).



To make eqn. (4) effective, it is necessary to minimize the two main competitive reactions of the *t*-BuO radical: hydrogen abstraction from C–H bonds in the reacting system [eqn. (8)] and reduction by the Fe(II) salt [eqn. (9)].



In order to minimize the side reaction of eqn. (8) we took 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 the *t*-BuO radical has been known for many years.⁶ Some data concerning hydrogen abstraction from cyclohexane are reported in Table 2. These data suggest that refluxing acetic acid should be particularly effective because, in addition to solvent and temperature effects, hydrogen abstraction from acetic acid is a relatively slow process, for polar

Table 2. Solvent and temperature effect on k_a/k_d [see eqns. (4) and (8)] with cyclohexane as the substrate.

Solvent	T/°C				
	100	70	40	25	0
C ₂ Cl ₄	4.14	11.1	39.9	87.8	293
Benzene	2.82	7.62	24.7	48.6	207
CH ₃ COOH	< 1	1.34	2.9	4.87	12.6

reasons. To minimize reaction (9) it was important to keep the steady-state concentration of Fe(II) salt in the reacting system low. This was achieved by using small amounts of Fe(III) acetate as a catalyst. Since no reaction occurs, under the same conditions, in the absence of an Fe(III) salt, the initiation of the redox chain seems to be substantially due to reaction (10), whereas the initiation by thermal decomposition of the hydroperoxide is negligible

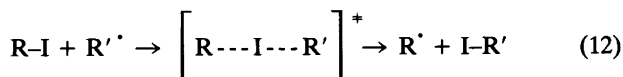
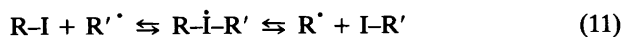


in refluxing acetic acid. This step is much slower than those of eqns. (5) and (9), so that the stationary concentration of the Fe(II) salt remains very low during the reaction.

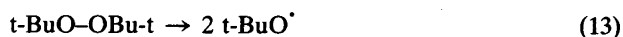
In this way we have developed a simple and effective procedure for the alkylation of heteroaromatic bases with primary and secondary alkyl iodides; some results are reported in Table 3. The procedure is less suitable for *t*-alkyl iodides, due to competitive side reactions, which do not lead to the corresponding alkyl radicals.

The high selectivity of the process was shown by competition between primary and secondary alkyl iodides: by using equimolar amounts of the two iodides, only alkylation by the secondary alkyl radical was observed. This result again supports the fact that combined enthalpic effects, which govern the equilibrium given in eqn. (1), and

polar effects, which govern the rates of eqn. (6), contribute to the high selectivity of the overall process. Recently, we¹⁰ suggested that this high selectivity could be related to the fact that the mechanism of the iodine abstraction could be an addition-elimination process [eqn. (11)] instead of the



classical atom-transfer process [eqn. (12)]. We have also effectively utilized (t-BuO)₂ for the heteroaromatic substitution by alkyl iodides in a purely thermal process. It is well known¹¹ that (t-BuO)₂ decomposes in the gas phase and in solution in many solvents at the same rate, which clearly indicates that no induced decomposition occurs. Only the homolysis of the -O-O- bond determines the overall decomposition rate, in contrast with the behaviour of most other peroxides.



However, in the presence of a protonated heteroaromatic base and alkyl iodide, the reaction leads to the selective alkylation of the heteroaromatic base [eqn. (14)] (Table 4).

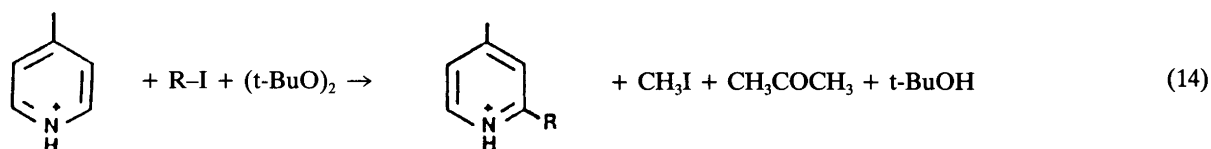


Table 3. Alkylation of heteroaromatic bases by alkyl iodides and t-BuOOH.

Heteroaromatic base	Alkyl iodide	Orientation (%)	Conversion (%)	Yields (%) ^a
Lepidine	Bul	2	86	84
Lepidine	<i>i</i> -PrI	2	96	94
Lepidine	<i>o</i> -C ₆ H ₁₁ I	2	92	93
Lepidine	<i>i</i> -Bul	2	95	93
Quinaldine	Bul	4	78	87
Quinaldine	<i>i</i> -PrI	4	70	92
Quinaldine ^b	<i>i</i> -PrI	4	100	91
Quinaldine	<i>o</i> -C ₆ H ₁₁ I	4	68	90
Quinoline	Bul	2 (30), 4 (32), 2,4 (38)	79	94
Isoquinoline	<i>i</i> -PrI	1	100	86
Isoquinoline	<i>o</i> -C ₆ H ₁₁ I	1	100	93
Acridine	<i>i</i> -PrI	9	85	90
4-Cyanopyridine	<i>i</i> -PrI	2 (71), 2,6 (29)	78	81
4-Cyanopyridine	<i>o</i> -C ₆ H ₁₁ I	2 (68), 2,6 (32)	74	83
4-Acetylpyridine	<i>i</i> -PrI	2 (65), 2,6 (35)	76	87
Quinoxaline	<i>i</i> -PrI	2 (53), 2,3 (47)	78	89
Quinoxaline	<i>o</i> -C ₆ H ₁₁ I	2 (62), 2,3 (38)	72	91
Benzothiazole	<i>i</i> -PrI	2	68	84
Benzothiazole	<i>o</i> -C ₆ H ₁₁ I	2	72	88

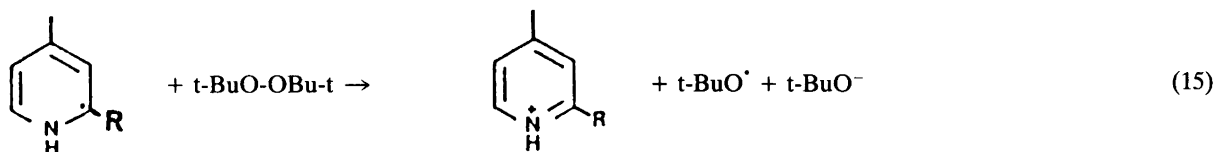
^aBased on the converted base. ^bThe amount of t-BuOOH was doubled.

Table 4. Alkylation of heteroaromatic bases by alkyl iodides and (t-BuO)₂.

Heteroaromatic base	Alkyl iodide	Orientation (%)	Conversion (%)	Yields (%)
Lepidine	C ₆ H ₁₃ I	2	85	87
Lepidine	2-C ₆ H ₁₃ I	2	100	85
Lepidine	c-C ₆ H ₁₁ I	2	100	89
Quinaldine	C ₆ H ₁₃ I	4	78	82
Quinaldine	2-C ₆ H ₁₃ I	4	95	86
Quinaldine	c-C ₆ H ₁₁ I	4	91	81
Isoquinoline	c-C ₆ H ₁₁ I	1	87	92
4-Cyanopyridine	c-C ₆ H ₁₁ I	2 (45), 2,6 (55)	88	83
Quinoxaline	c-C ₆ H ₁₁ I	2	72	78
Benzothiazole	c-C ₆ H ₁₁ I	2	68	81

At the same time, the rate of decomposition of (t-BuO)₂ is somewhat increased, as if a chain process, quite unusual with this peroxide, were involved. The relatively high temperature (ca. 130 °C) necessary for significant initiation favours the process, making the decomposition of the t-BuO[•] radical [eqn. (4)] (Table 4) effective.

The strongly reducing character of the pyridinyl radical⁵ formed in eqn. (6) would support the hypothesis of induced decomposition [eqn. (15)] of the peroxide.



The ionization energies of α -aminoalkyl radicals (5.4–5.7 eV)⁷ are lower by more than 2 eV than those of simple alkyl radicals; they are similar to those of lithium (5.39 eV) and sodium (5.14 eV), which explains why the pyridinyl radical behaves as a strong reducing agent toward (t-BuO)₂ [eqn. (15)].

These new methods of alkylation of heteroaromatic bases are particularly useful because of the general character of the reaction, the cheap reagents and the simple experimental conditions. The conversions reported in Tables 3 and 4 can be further increased by simply increasing the amount of peroxide. Thus quinaldine gives, with isopropyl iodide, a 70% conversion and a 92% yield, based on unrecovered quinaldine, according to the general procedure reported in the experimental section; however, the conversion of quinaldine becomes complete, with largely unchanged yields, simply by doubling the amount of t-BuOOH.

Experimental

All the reaction products were identified by comparison (GLC, NMR, MS) with authentic samples, prepared by a

different procedure developed by us¹² (alkylation by silver-catalyzed decarboxylation of carboxylic acids by persulfate).

General procedure with t-BuOOH. 2.5 mmol of the heteroaromatic base, 2.5 mmol of CF₃COOH, 5 mmol of t-BuOOH, 7.5 mmol of alkyl iodide and 0.12 mmol of Fe(III) acetate in 25 ml of AcOH were refluxed for 4 h. The solution was made basic with NaOH and extracted with CH₂Cl₂. The reaction products were analyzed by GLC, according to the same procedure previously utilized (quinaldine or lepidine as an internal standard). A competitive experiment was carried out by using lepidine and equimolar amounts of BuI and i-PrI; only 2-isopropyllepidine was observed by GLC, with no significant amounts of 2-butyllepidine.

General procedure with (t-BuO)₂. 2.5 mmol of the heteroaromatic base, 2.5 mmol of CF₃COOH, 7.5 mmol of alkyl iodide, and 7.5 mmol of (t-BuO)₂ in 25 ml of chlorobenzene were refluxed for 12 h. The solution was washed with 10% NaOH and analyzed as in the previous procedure.

References

1. Minisci, F. *Top. Curr. Chem.* 62 (1976) 1.
2. Minisci, F. In: Viehe, H. G., Ed., *Substituent Effects in Radical Chemistry*, Reidel, Dordrecht 1986, p. 391.
3. Minisci, F. and Vismara, E. In: Chizhov, O., Ed., *Organic Synthesis: Modern Trends*, Blackwell, Oxford, U.K. 1987, p. 229.
4. Minisci, F., Vismara, E. and Fontana, F. *Heterocycles* 28 (1989) 489.
5. Minisci, F., Vismara, E., Fontana, F., Morini, G. and Serravalle, M. *J. Am. Chem. Soc.* 106 (1984) 7146.
6. Fontana, F., Minisci, F. and Vismara, E. *Tetrahedron Lett.* 29 (1988) 1975.
7. Hawari, J. A., Kanabus-Kaminska, J. M., Wayner, D. D. and Griller, D. In: Viehe, H. G., Ed., *Substituent Effects in Radical Chemistry*, Reidel, Dordrecht 1986, p. 81.
8. Landolt-Börnstein *Radical Reaction Rates in Liquids*, Springer Verlag, Berlin 1984, pp. 6-8.
9. Walling, C. and Wagner, P. J. *J. Am. Chem. Soc.* 86 (1964) 3368.
10. Minisci, F., Vismara, E. and Fontana, F. *J. Org. Chem.* *In press.*
11. Walling, C. *Free Radicals in Solution*, Wiley, New York 1957, p. 469.
12. Minisci, F., Bernardi, R., Bertini, F., Galli, R. and Perchinunno, M. *Tetrahedron* 27 (1971) 35.

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