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Mechanism of the Gif-Barton type alkane functionalization by halide and pseudohalide ions.

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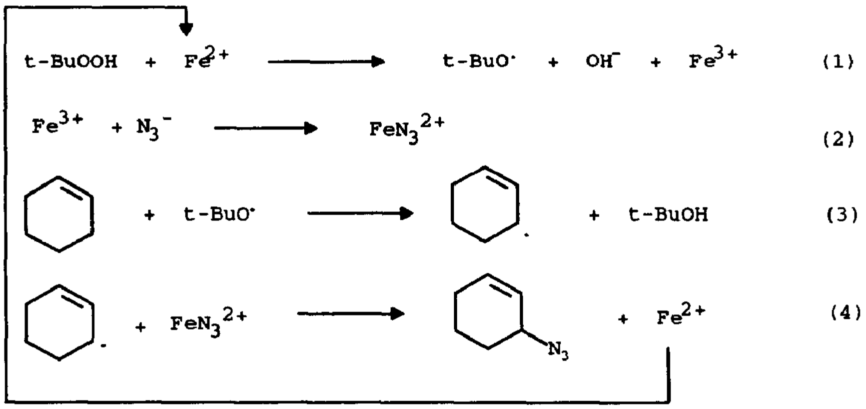
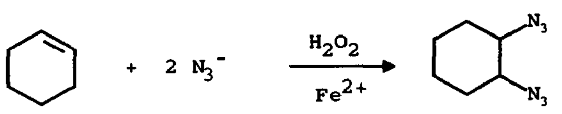
Abstract: The functionalization of alkanes by halide ions under the conditions of a Gif system can be explained by free-radical redox processes. The evidence is provided by trapping the intermediate alkyl radical by protonated heteroaromatic bases.

Very recently, D.H.R.Barton and coworkers[1] have reported the functionalization of alkanes by halide and pseudohalide ions (Cl, Br, N_3, SCN, etc.) under the conditions of a Gif system (t-BuOOH, Fe(III), pyridine, AcOH). The mechanism was not discussed in detail; however, it was stated that "in two cases the products define the mechanism". Particularly, it was reported that "the allylic azidation process is not a radical reaction, because anodically generated azide radicals add to cyclohexene to give 1,2-diazide with little allylic azide".
Many years ago we had reported[2] that the allylic azidation of cyclohexene and the benzylic azidation of toluene by the t-BuOOH/Fe(II)/N_3^- system occur through the free-radical redox chain mechanism of eqs.1-4.



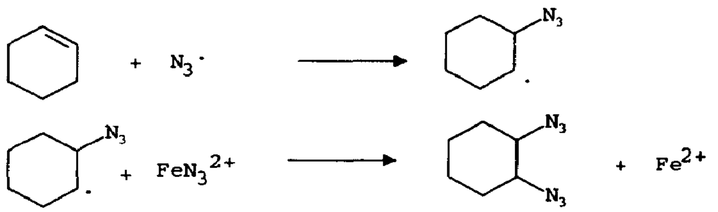
The use of H_2O_2 instead of t-BuOOH under the same conditions leads to a completely different reaction (eq.5), due to the fast oxidation of the azide ion by the hydroxyl radical[2,3] (eqs. 6-8)



(5)

The mechanism is quite similar with toluene. The difference between the Gif system and our procedure concerns the experimental conditions, and above all the use of Fe(III) instead of Fe(II) salt. However, we considered the possibility that Barton's results with cyclohexene and cyclohexane could also be explained by the mechanism of eqs.1-4, since several oxidation states of iron are always present in the redox system t-BuOOH/Fe(II).

$$N_3^- + {}^\cdot OH \longrightarrow N_3^\cdot + OH^- \qquad (6)$$


(7)

(8)

In order to obtain evidence of this mechanism, a key point is the unambiguous interception of alkyl radicals; for this purpose, we have taken advantage of the diagnostic criterion, often utilized by us for revealing the presence of nucleophilic alkyl radicals in a reacting system, namely their capture by protonated heteroaromatic bases[4].

Actually, a thorough analysis of the Barton conditions with cyclohexane in the absence of halide ions revealed the presence of 2- and 4-cyclohexylpyridines in significant amounts (31% based on t-BuOOH). These products certainly indicate the formation of intermediate cyclohexyl radical.The yields of cyclohexyl pyridines are satisfactory considering the acidity of the medium (a large excess of pyridine, 30 mL, compared with acetic acid, 3 mL), which plays a fundamental role in trapping alkyl radicals: the reactivity of protonated heteroaromatic bases towards alkyl radicals is 3-6 orders of magnitude higher compared with unprotonated bases, the phenomenon increasing from primary to secondary and tertiary alkyl radicals[4]. By using THF instead of cyclohexane, the corresponding α-tetrahydrofuranyl pyridines were obtained.

We also slightly modified Barton's conditions by using 15 mL of pyridine and 15 mL of quinoline instead of 30 mL of pyridine (quinoline is more reactive than pyridine[4] towards alkyl radicals), all the other conditions being unchanged: 2- and 4-cyclohexylquinolines were always formed in significant amounts together with minor amounts of 2- and 4-cyclohexylpyridines and 2- and 4-methylquinolines (Table). The formation of these latter compounds indicates with certainty the intermediate formation of t-BuO· radical, well known[5] to give rise to a competition between β-fission (t-BuO· $\longrightarrow$ MeCOMe + Me·) and hydrogen abstraction from cyclohexane, the latter largely prevailing in non protic solvents[5]. Analogous results were obtained by using 4-methylquinoline and quinoxaline instead of quinoline (Table).

All these results suggest that the formation of alkyl radicals is a major pathway under the Gif-Barton conditions and the mechanism of the reaction is well explained by the redox chain of eqs.1-4, which could be initiated by a slow interaction like the one in eq.9.

$$\text{t-BuOOH} + \text{Fe(III)} \longrightarrow \text{t-BuO}^\cdot + \text{Fe(IV)=O} + H^+ \qquad (9)$$

Table. Reaction of alkyl radicals with heteroaromatic bases.

Heteroaromatic base	Reagent	2-Isomer (%)[a]	4-Isomer (%)[a]	Yields (%)[f]
Pyridine[b]	Cyclohexane	64	36	33
"[c]	THF	79	21	30
Quinoline[d]	Cyclohexane	48	52	31
Lepidine[e]	"	100	--	21
Quinoxaline[e]	"	100	--	15

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

b) Barton conditions: cyclohexane (5 mmol), pyridine (3 mL), acetic acid (0.3 mL), $Fe(NO_3)_2 \cdot 9H_2O$ (0.5 mmol), TBHP (1 mmol), 60°C, 18h.

c) mmol of THF instead of cyclohexane.

d) as procedure b) with 1.5 mL of quinoline and 1.5 mL of pyridine instead of 3 mL of pyridine; 3% of 2-cyclohexylpyridine, 2% of 4-cyclohexylpyridine, 0.4% of quinaldine and 0.6% of lepidine were also formed.

e) as procedure d).

f) yields based on TBHP utilized.

The coordination of pyridine with Fe(III) salt could make this oxidation easier by increasing the electron availability of the Fe(III) salt. All the steps of this mechanism are well defined in free-radical chemistry; in several cases we[6] reported evidence for the formation of t-BuO· radical by reaction of Fe(III) acetate with t-BuOOH. The hydrogen abstraction from cyclohexene and cyclohexane by t-BuO· is well documented[5]. The interactions of alkyl radicals with halide and pseudohalide ions in the presence of iron or copper salts (eq.10) were first reported by this laboratory[7] and the masterly work of J.K.Kochi[8] has shown that these are very fast processes, which successfully compete with the attack by alkyl radicals onto the pyridine ring; ferric and cupric halides are among the most effective traps for alkyl radicals.

$$R^{\cdot} + FeX^{2+}\ (CuX^{+}) \longrightarrow R\text{-}X + Fe^{2+}\ (Cu^{+}) \qquad (10)$$

$$k = 10^{6} - 10^{9}\ M^{-1}s^{-1}$$

$$X = Cl,\ Br,\ I,\ SCN,\ CN,\ N_3\ etc.$$

On the other hand, Barton and coworkers[1] have reported that, in the oxidation of adamantane with H_2O_2 under Gif conditions, 2- and 4-adamantyl pyridines are formed in addition to chloroadamantanes. Moreover, in the following article[9] Barton and Hill report that chlorination of cyclooctane and alkylation of pyridine are competitive processes also in the oxidation of cyclooctane with t-BuOOH under Gif conditions, alkylation decreasing at higher Cl^- concentrations. We think that these results, too, are in good agreement with our interpretation and that the higher efficiency of the chlorination can be explained by the higher kinetic length of the redox chain, the regeneration of Fe(II) being much more effective in ligand transfer oxidation (eqs.4 and 10) than in heteroaromatic substitution[4].

Other possible competitive processes, such as the oxidation of halide ions to the corresponding radicals (e.g. $Br^- \xrightarrow{-e} Br^{\cdot}$), the equilibria between transient organo-iron intermediates and alkyl radicals and the oxidation of alkyl radicals or alkanes according to eqs. 9 and 10 could explain particular aspects of the reaction, always involving alkyl radical intermediates, but the general functionalization by halide and pseudohalide ions is well explained by the known free-radical chemistry.

$$R^{\cdot} + Fe(IV)=O + H^{+} \longrightarrow R\text{-}OH + Fe(III) \quad (\text{or } R^{+} + Fe(III)OH) \qquad (11)$$

$$R\text{-}H + Fe(IV)=O \longrightarrow R^{\cdot} + Fe(III)OH \qquad (12)$$

Carbonium ion can simply explain the low-efficiency formation of cyclooctene and cyclooctyl t-butyl peroxide in the oxidation of cyclooctane with t-BuOOH[9]. Cyclooctanol and cyclooctanone can be formed by decomposition of the peroxide.

REFERENCES

1. Barton, D.H.R.; Bévière, S.D.; Chavasiri, W.; Doller, D.; Hu, B. *Tetrahedron Lett.* **1993**, *34*, 1871; Barton, D.H.R.; Bévière, S.D. *Tetrahedron Lett.* **1993**, *34*, 5689.

2. Minisci, F.; Galli, R.; Cecere, M. *Gazz.Chim.Ital.* **1964**, *94*, 67.

3. Minisci, F.; Galli, R. *Tetrahedron Lett.* **1962**, 533; *ibid.* **1963**, 357; Minisci, F. *Chim.Ind. (Milan)* **1967**, *49*, 706; Minisci, F. *Acc.Chem.Res.* **1975**, *8*, 165.

4. Minisci, F.; Fontana, F.; Vismara, E. *J.Heterocycl. Chem.* **1990**, *27*, 79; *Heterocycles* **1989**, *28*, 489.

5. Walling, C.; Wagner, P.J. *J.Am.Chem.Soc.* **1964**, *86*, 3368.

6. Fontana, F.; Minisci, F.; Nogueira Barbosa, M.C.; Vismara, E. *Acta Chem.Scand.* **1989**, *43*, 995; Coppa, F.; Fontana, F.; Minisci, F.; Nogueira Barbosa, M.C.; Vismara, E. *Tetrahedron* **1991**, *47*, 7343; Minisci, F.; Fontana, F.; Pianese, G.; Yan, Y.M. *J.Org.Chem.* **1993**, *58*, 4207.

7. Minisci, F. *Ital.Pat. N.* 2881 (17/5/1957); *Angew.Chem.* **1958**, *70*, 599; *Gazz.Chim.Ital.* **1959**, *89*, 626, 1910, 1922, 1941, 2428, 2438.

8. Kochi,J.K. in *Free Radicals*, Kochi, J.K., ed.; John Wiley and Sons, Inc.: New York, 1973; p. 591.

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