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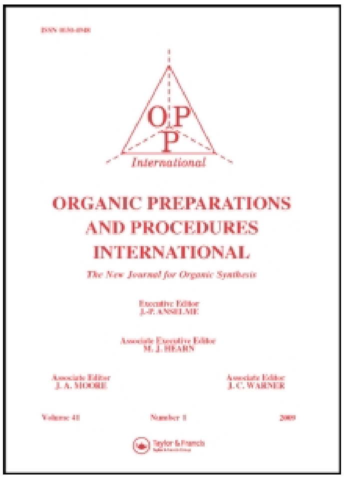

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A NEW PROCEDURE FOR THE SELECTIVE α-OXYALKYLATION OF HETEROAROMATIC BASES BY CYCLIC ETHERS AND HYDROGEN PEROXIDE

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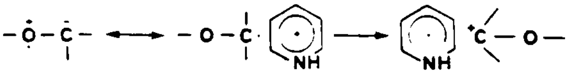
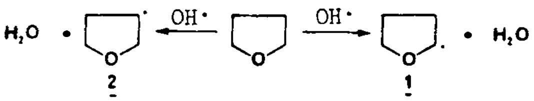
The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is of great synthetic interest in that it reproduces most of the numerous aspects of the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity.[1] The protonation of the base strongly increases its reactivity towards nucleophilic species.[2] The nucleophilic character of the alkyl radicals is increased by the presence of an ether oxygen in α-position, due to conjugation in the ground state and to the stability of the α-alkoxycarbonium ions as contribution of polar forms in the transition state (Eq.1).[1,3] Thus , α-alkoxy radicals are particularly suitable for heteroaromatic substitution.

 (1)

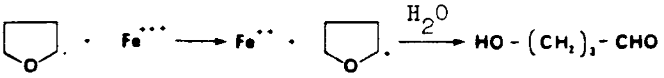
A variety of oxidants such as H_2O_2,[4] t-BuOOH,[4] $S_2O_8^{=}$,[4] $(PhCOO)_2$,[5] dialkylpercarbonate,[4] $^{+}NH_3OSO_3^{-}$,[6] and $^{+}NH_3OH$ [7] have been utilized to generate α-oxyalkyl radicals from cyclic ethers. H_2O_2 is the simplest and the least expensive among these oxidants. Thermal or photochemical decomposition of H_2O_2 in ethers, such as dioxane or THF, gives very poor results; better results can be obtained by redox decomposition of H_2O_2 by Fe (II) salt.[4] However, the redox decomposition is characterized by two main disadvantages:

a) The intermediate·OH radical is not selective in hydrogen abstraction.[8] Thus, with dioxane there is no problem of regioselectivity in hydrogen abstraction, but with THF both the hydrogen atoms in the α- and β-positions are involved (Eq. 2) and both the radicals 1 and 2 give the corresponding substitution products.



(2)

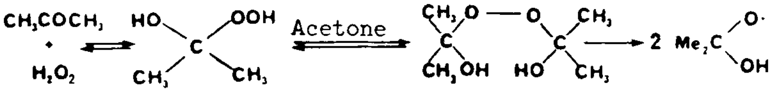
b) The Fe (III) salt oxidizes the α- alkoxy radical 1 rapidly (Eq. 3) and this reaction competes with the heteroaromatic addition.[5] In contrasts ra-



(3)

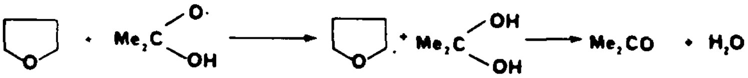
dical 2 is not oxidized and the ratio of the products obtained from 1 and 2 is thus strongly dependent on the concentration of Fe (III) salt.[7]

We now report a new procedure, in which acetone is used as solvent together with cyclic ethers. No metal salt is required in this procedure,as the thermal decomposition is sufficient to generate α-alkoxy radicals useful for the heteroaromatic substitutions. No reaction occurs in the absence of acetone, even at higher temperatures (boiling dioxane). The procedure is very simple and the results are summarized in the Table. We suggest that the function of acetone is to add H_2O_2 as depicted in Eqs. 5 and 6. It is well known[8] that acetone and H_2O_2 give a mixture of peroxides and compound 3 predominates in the presence of an excess of acetone.



(4)

Since no reaction occurs in the absence of acetone it is reasonable to suppose that the thermal homolysis of peroxide 3 is much faster than that of H_2O_2 so that the equilibria of Eq. 4 are shifted towards 3. Moreover the alkoxy radicals are much more selective than the hydroxyl radical in hydrogen abstraction[8] (Eq. 5) as shown by the fact that with THF the substitution products arise mainly from 1 with only traces of products from 2. Compared to H_2O_2, peroxide 3 has the further advantage that it is much less susceptible to a chain decomposition.



(5)

Lepidine and isoquinoline which have only one position of high nucleophilic reactivity give only one monosubstituted isomer (in position 2- and 1- respectively). 4-Cyanopyridine has two equivalent positions of high nucleophilic reactivity (2- and 6-) and, as the conversions increase, the 2,6-disubstituted derivatives are formed. The procedure appears to be quite general for heteroaromatic bases and cyclic ethers.

EXPERIMENTAL SECTION

General Procedure.- A solution of 2 mmoles of heteroaromatic base, 2 mmoles of CF_3COOH and 6 mmoles of 60% H_2O_2(caution!) in 5 ml of acetone and 5 ml of dioxane (or THF) was refluxed for 10 hrs. The solution was then diluted with 20 ml of water, made basic with conc.ammonia, extracted by CH_2Cl_2 and analyzed by GLC (Analytical GLC analyses were performed with a Carlo Erba 4200 instrument equipped with flame ionization detector, column OV 17 3% on Chromosorb W HP 100-120 mesh, length 2.5 m, programm 120°C, 2 min., 20 C/min., 240°, internal standard quinaldine or lepidine). The results are reported in the Table. The reaction products were isolated by flash chromatography on silica gel(hexane:MeCOOEt 1:1, v:v) and identified by direct comparison with authentic samples (NMR, MS, IR) previously obtained by different procedures.[4,6,7]

TABLE. Substitution of Heteroaromatic Bases by Dioxane and THF

Heteroaromatic base	Ether	Reaction products	Conversion (%)	Yield[a] (%)
Lepidine	THF	2-(α-tetrahydrofuranyl) lepidine	58	97
Lepidine	Dioxane	2-dioxanyllepidine	59	62
Isoquinoline	THF	1-(α-tetrahydrofuranyl) isoquinoline	62	81
Isoquinoline	Dioxane	1-dioxanylisoquinoline	78	64
4-Cyanopyridine	THF	2-(α-tetrahydrofuranyl) 4-cyanopyridine (70%) 2,6-di-(α-tetrahydrofunyl)-4-cyanopyridine(30%)	74	99
4-Cyanopyridine	Dioxane	2- dioxanyl-4-cyanopyridine (80%) 2,6-bis-dioxanyl-4-cyanopyridine (20%)	71	92

a) Yields based on converted heteroaromatic derivatives

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