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NEW GENERAL AND CONVENIENT SOURCES OF ALKYL RADICALS, USEFUL FOR SELECTIVE SYNTHESES

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Abstract- Alkyl radicals are obtained from alkyl iodides under very simple conditions and with cheap reagents: i) H_2O_2 and DMSO; ii) H_2O_2 and acetone; iii) t-BuOOH. The alkyl radicals can be utilized for selective syntheses, mainly selective formation of carbon-carbon bonds.

Recent years have brought a rapid development in the use of alkyl radicals for the selective syntheses of C-C bonds and in the synthesis of target molecules[1]. The availability of new simple and cheap sources of alkyl radicals is therefore of undoubted synthetic interest. We report in this communication new very convenient and versatile sources of alkyl radicals and their use in selective syntheses.

The basic idea arose from recent kinetic and thermodynamic results[2] reported by D. Griller for the reaction of alkyl radicals with alkyl iodides (eq.1)

$$R\text{-}I + R'\cdot \rightleftarrows R\cdot + R'\text{-}I \qquad (1)$$

The rate constants for the forward and back reactions (1) are normally $>10^6 M^{-1}s^{-1}$ and the equilibria are strongly shifted towards the more stable of the two alkyl radicals R. and R'.. Thus the idea was to use a simple and cheap source of methyl radical (the least stable among the alkyl radicals) to generate selectively alkyl radicals of any kind.

Alkylation of protonated heteroaromatic bases. The homolytic alkylation of heteroaromatic bases is a general reaction of great synthetic interest, due to the high regio- and chemo-selectivity[3]. We have developed three new effective methods, based on the above-mentioned concept:

A) H_2O_2 is added to a solution of alkyl iodide, protonated heteroaromatic base and a catalytic amount of $FeSO_4$ in DMSO. The stoichiometry of the reaction is shown by eq. (2).

$+ \text{R-I} + H_2O_2 + CH_3SOCH_3 \quad \overset{Fe^{2+}}{\underset{Fe^{3+}}{}} \quad + CH_3I + CH_3SO_2H + H_2O$ (2)

The mechanism of the reaction is shown by Scheme 1

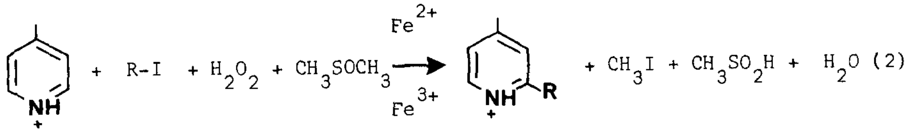
$H_2O_2 + Fe^{2+}$ HO. + HO^- + Fe^{3+}

HC O.

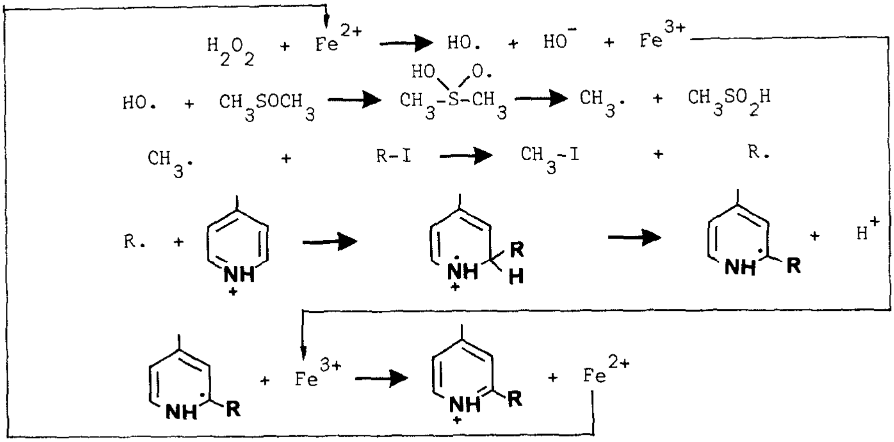
HO. + CH_3SOCH_3 $CH_3\text{-S-}CH_3$ CH_3. + CH_3SO_2H

CH_3. + R-I $CH_3\text{-I}$ + R.

R. + + H^+

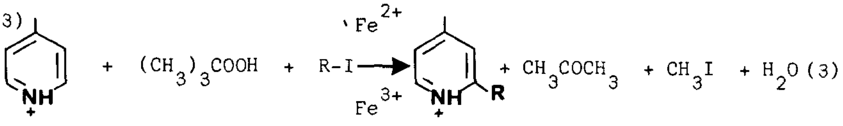


The mechanism of the reaction is shown by Scheme 1



Scheme 1

eq. (3)



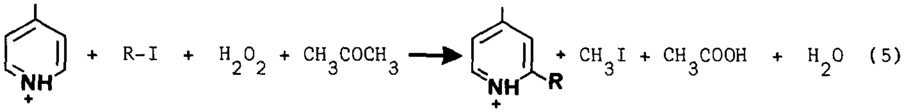
The mechanism is similar to that of Scheme 1; the only difference is in the generation of the methyl radical (eq.4)

$$(CH_3)_3COCH + Fe^{2+} \longrightarrow Fe^{3+} + OH^- + (CH_3)_3CO. \longrightarrow CH_3 + CH_3COCH_3 \quad (4)$$

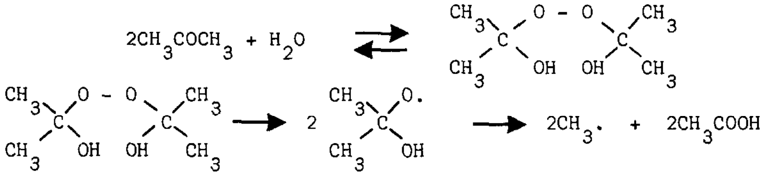
Experimental procedure: A solution of 2.5 mmol of lepidine, 5 mmol of CF_3COOH, 5 mmol of t-BuOCH, 12.5 mmol of isopropyl iodide and 0.25 mmol of $Fe(OAc)_2OH$ in 25 ml of acetic acid was refluxed for 4 hrs.

The solution was diluted with water, made basic with NaOH, extracted with CH_2Cl_2 and analyzed by g.l.c. (quinaldine as internal standard). Conversion: 90%; yield of 2-isopropyl-4-methylquinoline (identified by comparison with an authentic sample), based on converted lepidine: 92%.

C) H_2O_2, alkyl iodides and protonated heteroaromatic bases are refluxed in acetone (eq.5)



The formation of the methyl radical is shown by Scheme 2



Scheme 2

Experimental procedure: A solution of 2.5 mmol of lepidine, 7.5 mmol of H_2O_2, 12.5 mmol of isopropyl iodide and 7.5 mmol of CF_3COOH in 25 ml of acetone was refluxed for 24 hrs. The solution was diluted with water, made basic with NaOH and extracted with CH_2Cl_2. Conversion of lepidine: 55%. Yield of 2-isopropyl-4-methylquinoline: 75% (based on converted lepidine).

The procedures A,B and C have general character with primary, secondary and tertiary alkyl iodides and protonated heteroaromatic bases with free positions of high nucleophilic reactivity (α and γ). No significant attack of the methyl radical to the heterocyclic ring is observed (the iodine abstraction is faster).

Free-radical diazo-coupling. Nucleophilic alkyl radicals arising according to Scheme 1 add very fast to diazonium salts giving the diazo-coupling reaction (eqs.6 and 7):

$$R\cdot + N{\equiv}N^{+}\text{-}Ar \longrightarrow R\text{-}N{=}N^{+}\text{-}Ar \qquad (6)$$

$$R\text{-}N{=}N\text{-}Ar + Fe^{2+} \longrightarrow R\text{-}N{=}N\text{-}Ar + Fe^{3+} \qquad (7)$$

Stoichiometric amounts of Fe(II) salt are required in this case and the overall stoichiometry is shown by eq (8)

$$ArN_2^{+} + RI + CH_3SOCH_3 + H_2O_2 + 2Fe^{2+} \longrightarrow$$
$$\longrightarrow Ar\text{-}N{=}N\text{-}R + CH_3I + CH_3SO_2H + H_2O + 2Fe^{3+} \qquad (8)$$

The reaction has general character for diazonium salts and primary, secondary and tertiary alkyl iodides. The procedure is much more convenient than that previously developed by us[4], in which the theoretical yield based on diazonium salt is 50% (eq.9)

$$2ArN_2^+ + RI + 2Ti^{3+} \longrightarrow Ar\text{-}N{=}N\text{-}R + ArI + N_2 + 2Ti^{4+} \quad (9)$$

Typical procedure: 296 mg of $NaNO_2$ in 2.5 ml of water were added under stirring at 0 C to a solution of 500 mg of p-chloroaniline in 7.5 ml of 10% H_2SO_4 ; then 4.4 g of $FeSO_4.7H_2O$ and 2 ml of t-BuI in 80 ml of DMSO were added at 0-5°C. The solution was diluted with water and extracted with hexane. G.l.c. analysis (p-chlorotoluene as internal standard) revealed the presence of p-chlorophenyl-t-butyl-diazene in 70% yield, based on used p-chloroaniline. The product was identified by comparison with an authentic sample.

Nucleophilic alkyl radicals, generated according the procedure A,B and C are also effective in the alkylation of pyrylium[5] and iminium[6] salts, biacetyl[7] ($R\text{-}I \rightarrow R\text{-}COCH_3$) , quinones[7], oximes[8], alternating addition to conjugated olefins[9], already developed by different radical sources (Refs. 5-9). Moreover the method is still effective in generation of electrophilic alkyl radicals by iodine abstraction from easily available derivatives of general structure $I\text{-}CXR_2$ (X= electron-withdrawing group) and substitution of electron-rich aromatics and inter- and intra-molecular addition to olefins[9]. Full papers will report the details of the great synthetic potential by using these new simple, cheap and selective sources of alkyl radicals. .

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