

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

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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<sup>1</sup>. 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.

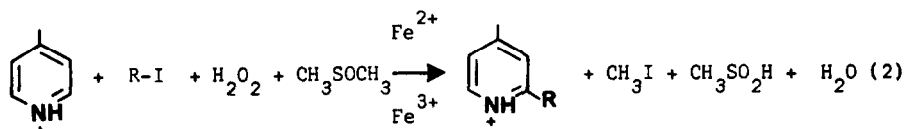
The basic idea arose from recent kinetic and thermodynamic results<sup>2</sup> reported by D. Griller for the reaction of alkyl radicals with alkyl iodides (eq.1)



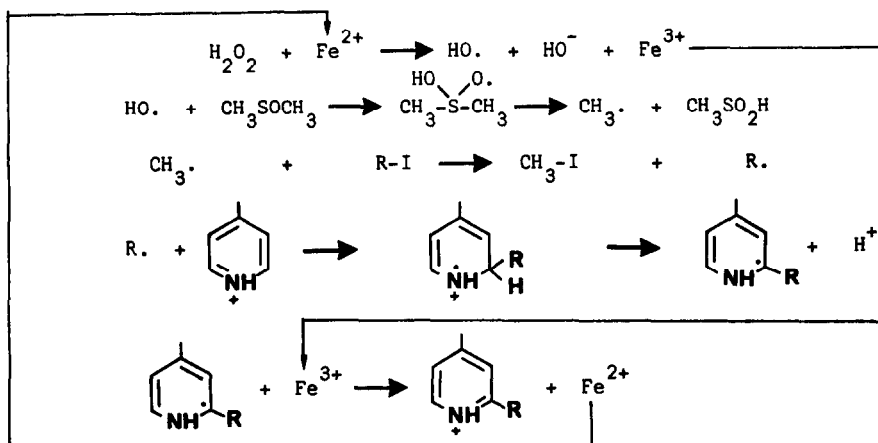
The rate constants for the forward and back reactions (1) are normally  $>10^6 M^{-1} s^{-1}$  and the equilibria are strongly shifted towards the more stable of the two alkyl radicals R. and R'.. Thus the idea was to use a simple and cheap source of methyl radical (the least stable among the alkyl radicals) 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<sup>3</sup>. 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).

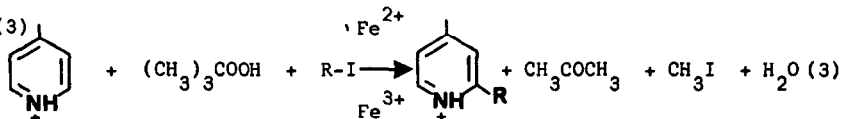


The mechanism of the reaction is shown by Scheme 1

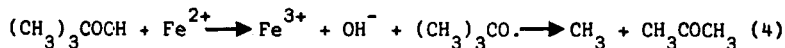


The following procedure is representative: 5 mmol of 30%  $\text{H}_2\text{O}_2$  were added dropwise over 5 min. at room temperature to a stirred solution of 2.5 mmol of quinaldine, 2.5 mmol of  $\text{H}_2\text{SO}_4$ , 7.5 mmol of cyclohexyl iodide and 0.5 mmol of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$  in 25 ml of DMSO. The solution was stirred for 15 min., diluted with water, made basic with NaOH and extracted with  $\text{CH}_2\text{Cl}_2$ . G.l.c. ( lepidine as internal standard ) gives a conversion of quinaldine of 90% and a yield of 2-methyl-4-cyclohexylquinoline, based on converted quinaldine, of 98%. The reaction product was identified by comparison with an authentic sample.

B) t-BuOOH reacts with alkyl iodides and heteroaromatic bases in acetic acid and in the presence of a catalytic amount of iron salt according to eq. (3)



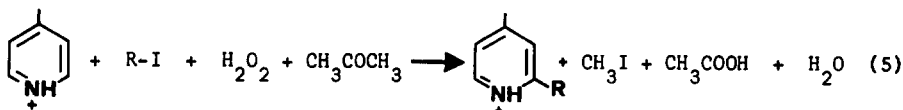
The mechanism is similar to that of Scheme 1; the only difference is in the generation of the methyl radical (eq.4)



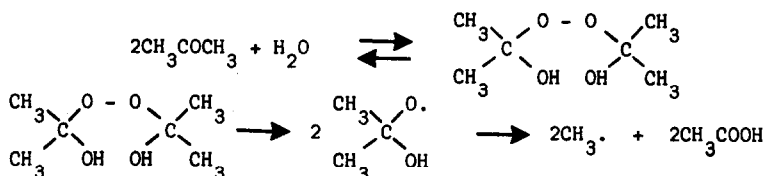
Experimental procedure: A solution of 2.5 mmol of lepidine, 5 mmol of  $\text{CF}_3\text{COOH}$ , 5 mmol of t-BuOOH, 12.5 mmol of isopropyl iodide and 0.25 mmol of  $\text{Fe}(\text{OAc})_2 \cdot \text{OH}$  in 25 ml of acetic acid was refluxed for 4 hrs.

The solution was diluted with water, made basic with NaOH, extracted with  $\text{CH}_2\text{Cl}_2$  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)  $\text{H}_2\text{O}_2$ , alkyl iodides and protonated heteroaromatic bases are refluxed in acetone (eq.5)



The formation of the methyl radical is shown by Scheme 2



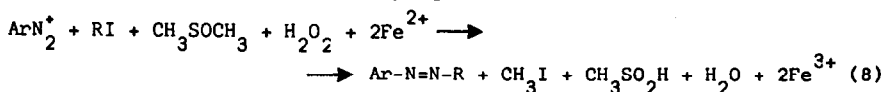
Scheme 2

Experimental procedure: A solution of 2.5 mmol of lepidine, 7.5 mmol of  $\text{H}_2\text{O}_2$ , 12.5 mmol of isopropyl iodide and 7.5 mmol of  $\text{CF}_3\text{COOH}$  in 25 ml of acetone was refluxed for 24 hrs. The solution was diluted with water, made basic with NaOH and extracted with  $\text{CH}_2\text{Cl}_2$ . 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 ( $\alpha$  and  $\gamma$ ). No significant attack of the methyl radical to the heterocyclic ring is observed ( the iodine abstraction is faster ).

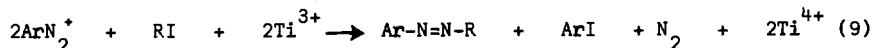
Free-radical diazo-coupling. Nucleophilic alkyl radicals arising according to Scheme 1 add very fast to diazonium salts giving the diazo-coupling reaction ( eqs.6 and 7 ):



Stoichiometric amounts of Fe(II) salt are required in this case and the overall stoichiometry is shown by eq (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<sup>4</sup>, in which the theoretical yield based on diazonium salt is 50% ( eq.9 )



Typical procedure: 296 mg of  $\text{NaNO}_2$  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%  $\text{H}_2\text{SO}_4$ ; then 4.4 g of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ , 8 mmole of  $\text{H}_2\text{O}_2$  (30%) 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<sup>5</sup> and iminium<sup>6</sup> salts, diacetyl<sup>7</sup> (  $\text{R-I} \rightarrow \text{R-COCH}_3$  ), quinones<sup>7</sup>, oximes<sup>8</sup>, alternating addition to conjugated olefins<sup>9</sup>, 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  $\text{I-CXR}_2$  ( X= electron-withdrawing group ) and substitution of electron-rich aromatics and inter- and intra-molecular addition to olefins<sup>9</sup>. 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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(Received in UK 14 September 1987)