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α-HYDROXYALKYLATION OF HETEROAROMATIC BASES BY ALCOHOLS AND HYDROXYLAMINE-O-SULPHONIC ACID

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Abstract—The homolytic decomposition of hydroxylamine-O-sulphonic acid in alcoholic solvents was investigated in the presence or absence of protonated heteroaromatic bases and Fe(II) salt. The addition of the α-hydroxyalkyl radicals to the base and their oxidation by Fe(III) salt to the corresponding alkyl cyanide were competitive processes. A redox chain process involving the amino radical cation, $NH_3^{+\cdot}$, is suggested and the factors affecting the yields of the homolytic substitution are discussed.

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centred free radicals is an important reaction for this class of compounds.

Polar effects, related to the nucleophilic character of the carbon-centred radicals, and the electron-deficiency of the protonated base play a relevant role in determining the synthetic success of these reactions.[1]

General free radical sources for aromatic substitution involve the initial formation of electrophilic radicals, which do not attack the heteroaromatic bases but can react with suitable substrates (i.e. alcohols) to generate nucleophilic radicals.[1]

Electrophilic oxygen-centred radicals have been largely used for this purpose. Electrophilic nitrogen-centred free radicals, especially if protonated, can, in principle, be used in this context.

Until now, however, their use has been restricted to N-chloroamines.[2] A severe limitation of this approach, is the competitive fast chlorine abstraction from N-chloroamine by the carbon-centred radical intermediates. To avoid this competitive reaction, we have considered the redox decomposition of hydroxylamine-O-sulphonic acid (HOSA) as source of amino radical cation (Eq. 1)

$$\overset{+}{N}H_3OSO_3^- + Fe^{2+} \rightarrow NH_3^{+\cdot} + SO_4^{2-} + Fe^{3+} \quad (1)$$

$$NH_3^{+\cdot} + RH \rightarrow R^{\cdot} + NH_4^+. \quad (2)$$

HOSA is an easily available and versatile reagent[3] and its use for free radical amination of olefins and aromatics in the presence of iron(II) has been previously reported by us.[4]

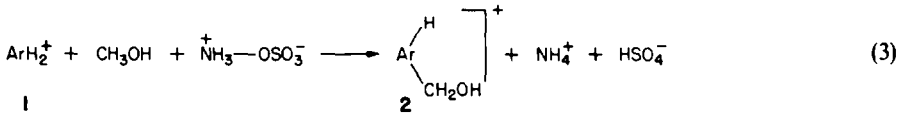
Now we have undertaken a general research concerning the formation of nucleophilic carbon radicals, suitable for the substitution of heteroaromatic bases, by hydrogen abstraction (Eq. 2) of the amino radical cation generated in Eq. 1.

Preliminary result with alcohols, ethers and amides, have been reported.[5]

In this work the behaviour of alcohols as hydrogen donors will be discussed.

RESULTS

When small amounts of iron(II) sulphate (3% based on HOSA) were added to a solution of HOSA and protonated heteroaromatic base in methanol–water solution at 20°, an exothermic process takes place and, in a few minutes, the HOSA is decomposed affording hydroxymethylation of the base (ArH_2^+) in α and γ positions of the heterocyclic ring (Eq. 3).



(3)

No reaction takes place in the absence of ferrous salt at this temperature.

Similar results have been accidentally obtained[6] by other authors in attempts to prepare 1-aminoquinolinium sulphate by HOSA in methanol. The surprising fact is that these authors report that "the hydroxymethylation reaction is unaffected by the presence or absence of ferrous ions". Thus we tried to reproduce their results in methanol in the absence of ferrous salt; unfortunately, the reaction temperature was not reported. We were forced to investigate the range from 20° to 64° (b.p. of methanol); no appreciable reaction takes place at temperature lower than 50° (Table 1). At 64° some hydroxymethylation of the base occurs, but the yields are poor (entry 5 of Table 1), significantly lower than those previously reported (entry 6). In any case, also the results reported in the absence of ferrous salt (entry 6), are much worse than those obtained in the presence of ferrous salt (entry 1 and 2); it is necessary to use 3 mols of HOSA for 1 mol of base in the absence of Fe^{2+} to obtain conversions and yields comparable with those obtained with 1 mol of HOSA in the presence of Fe^{2+}.

The reaction, in absence of Fe^{2+} salt, is also very sensitive to the acidity of the medium and the amount of water. Thus by using 4-methylquinoline hydrogen sulphate in methanol no reaction occurs (entry 3), but it is sufficient to use a methanol : water 95 : 5 ratio under the same conditions to have a moderate quinoline conversion to the corresponding 2-hydroxymethyl derivative **2** (entry 4). When ferrous sulphate was used in the presence of iron powder, in order to minimize the

Table 1. Hydroxymethylation of protonated heteroaromatic bases (ArH_2^+) by HOSA in MeOH[a]

Entry	ArH_2^+	Fe(II) (mmol)	BASE/HOSA (mmol)	Solvent MeOH/H_2O (ml)	T (°C)	Conv. (%)	Yield (%)[b]
1	Lepidine	0.12	4:4	8:4	20	70	61
2	Lepidine	4	4:4	20:15	20	51	81
3	Lepidine	—	4:12	10:0	64	—	—
4	Lepidine	—	4:12	15:0.7	60	65	88
5	Lepidine[e]	—	4:12	10:0	64	40	45
6	Lepidine[c,e]	—	4:12	10:0	64	76	68
7	Quinaldine	0.12	4:4	8:4	20	20.6	80.6
8	Quinaldine	0.12	4:12	8:4	20	55	90.9
9	Quinaldine	1.2	4:12	8:4	20	78	78.2
10	Quinaldine	1.2[d]	4:12	8:4	20	70	97
11	4-Cyanopyridine	0.12	4:4	4:2	20	35.9	78

[a] All reactions were carried out on 4 mmol of base in the presence of conc. H_2SO_4 (4 mmol) unless otherwise noted.
[b] Based on converted base.
[c] Ref. 6.
[d] Reaction carried out in the presence of powder iron (67 mg, 1.2 mmol).
[e] Without H_2SO_4.

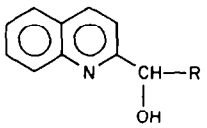
ratio Fe^{3+}/Fe^{2+}, a very high yield of **2** based on converted aromatic, and good yields based on HOSA, were obtained (entry 10). All the results obtained for three different bases are summarized in Table 1.

When the couple Fe^{2+}/Fe^{3+} was used in catalytic amounts to decompose HOSA in methanol in the presence of protonated bases, a decrease of the yield of **2** was observed but the effect was not dramatic.

With ethanol and n-butanol, under Fe^{2+} catalysis, only very poor yields of products of α-hydroxyalkylation of the base (**3**) and (**4**) were obtained without alkylation by the β-carbon radicals (Table 2, entry 14). However, significant amounts of acetonitrile and n-butyronitrile, respectively, were formed (Eq. 4). Similar results were also observed in the absence of Fe^{2+} and at higher temperature (Table 2, entries 13 and 12). A slight increase of yield of the α-hydroxyethyl derivative of lepidine was obtained by using iron powder (Table 2, entry 15).

$$RCH_2OH + 2\overset{+}{N}H_3OSO_3^- \rightarrow R{-}C{\equiv}N + NH_4^+ + 2HSO_4^- + H_3O^+ \quad (4)$$

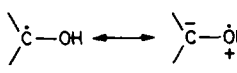
With isopropanol, no addition to the base was observed under all conditions.



3 R = CH_3
4 R = C_3H_7

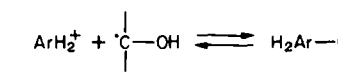
DISCUSSION

α-Hydroxyalkyl radicals have a particularly strong nucleophilic character as their standard redox potentials (−0.98, −1.18 V and −1.30 V for $\dot{C}H_2CH_2OH$, $CH_3\dot{C}HOH$ and $(CH_3)_2\dot{C}OH$, respectively)[7] and pK_a values (10.7, 11.5 and 12.03 for $\dot{C}H_2OH$, $CH_3\dot{C}HOH$ and $(CH_3)_2\dot{C}OH$, respectively, 4–5 units lower than the parent alcohols)[8] indicate. These characteristic features are the results of the electron-density distribution, which may be described by the resonance of the valence structure of Eq. 5.

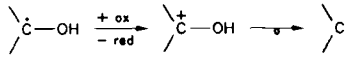

(5)

Therefore, a strong interaction between these radicals and protonated heteroaromatic bases should be expected. However, two main factors can influence the synthetic potential of the reaction:

(i) The stabilization by Eq. 5 can make reversible the addition of α-hydroxyalkyl radicals to the protonated heteroaromatic base (Eq. 6); the reversibility increasing, with decreasing of the strength of the bond formed, from hydroxymethyl to secondary and tertiary hydroxyalkyl radicals[9]


(6)

(ii) The high nucleophilic character determines a very fast oxidation of α-hydroxyalkyl radicals (Eq. 7) by a variety of oxidants, included the protonated heteroaromatic base itself (Eq. 8), especially with t-α-hydroxyalkyl radicals and bases of high electron affinity.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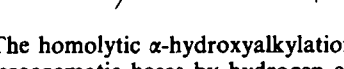

(8)

The homolytic α-hydroxyalkylation of protonated heteroaromatic bases by hydrogen abstraction from alcohols with oxygen-centred radicals (from H_2O_2, $S_2O_8^{--}$, t-BuOOH, peresters, etc.) has been reported.[10] Good results were obtained with methanol, poor with ethanol and no substitution was observed with isopropanol. The results using HOSA as source of

Table 2. Homolytic decomposition of HOSA in ethanol in the presence of lepidine (4 mmol) and H_2SO_4 (4 mmol)

Entry	Fe(II) (mmol)	BASE/HOSA	Solvent EtOH/H_2O	T (°C)	Yield (%) 2[a]	Yield (%) CH_3CN[b]
12[c]	—	4:12	10:0	78	1.1	17
13[c]	—	4:12	8:4	78	1.0	20
14	0.12	4:4	8:4	20	0.5	40
15[d]	0.12	4:4	8:4	13	3.0	64

[a] Based on starting lepidine (the recovered lepidine was practically quantitative).
[b] Based on HOSA.
[c] Without H_2SO_4.
[d] Reaction performed in the presence of Fe powder (67 mg, 1.2 mmol).

ammoniumyl radical ($\dot{N}H_3^+$) appear to follow a similar trend. No carbon free radicals different from α-hydroxyalkyls were trapped by the heteroaromatic base in agreement with the electrophilic behaviour of $\dot{N}H_3^+$ and with previous e.s.r. studies which used a different source of $\dot{N}H_3^+$ ($NH_2OH/Ti^{3+}/H^+$).[11] The reaction appears to be very sensitive to the medium and the best results were obtained only in the presence of iron(II) (Tables 1 and 2) and in a reducing medium.

Because iron(II) works as effective catalyst of HOSA decomposition in the presence of alcohols and heteroaromatic base, we explain the results obtained by the general redox-chain mechanism of Scheme 1.

In the absence of catalyst, at higher temperature, probably the free-radical chain of Scheme 2 takes place.

The lower efficiency of the chain reaction shown in Scheme 2 is determined in part by the initiation reaction which is slower in thermal than in the redox process and mainly by side ionic reactions of HOSA. Thus, HOSA fast hydrolyses[12] above 25° in medium containing water to yield hydroxylammonium cation and hydrogen sulphate anion (Eq. 9)

$$\overset{+}{N}H_3OSO_3^- + H_2O \rightarrow \overset{+}{N}H_3OH + HSO_4^- \quad (9)$$

and it is known that Fe^{2+} does not reduce the hydroxylammonium cation efficiently (in contrast to Ti^{+3}).[11] This reaction, therefore decreases the efficiency of the process and competes with the homolytic reaction more effectively under thermal than redox initiation.

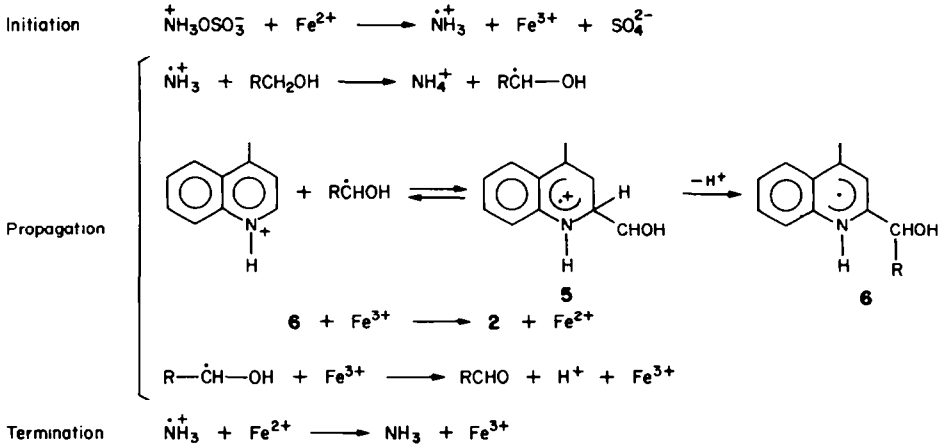
From the results of Table 1, it can be deduced that the radical $\dot{C}H_2OH$ must add efficiently to the base and that only the Fe^{3+} ion is responsible for its oxidation. Because the oxidation rate constants of $\dot{C}H_2OH$ by Fe^{3+} has been estimated[13] to be higher than 4×10^8 $M^{-1}\ s^{-1}$, the addition rate constant to protonated 4-methylquinoline must be in the range 10^7–10^8 $M^{-1}\ s^{-1}$.

The oxidation rates of $R\dot{C}HOH$ radicals by Fe^{3+} (and also by HOSA) are certainly higher than that of $\dot{C}H_2OH$, and the significant formation of the corresponding nitriles indicate that their oxidation prevails over the aromatic attack. Our failure to obtain good results in addition products both in thermal and catalyzed reaction, however, could be explained more by a relevant contribute of the reversibility of the addition to the aromatic ring than by a reduction in the addition rate.

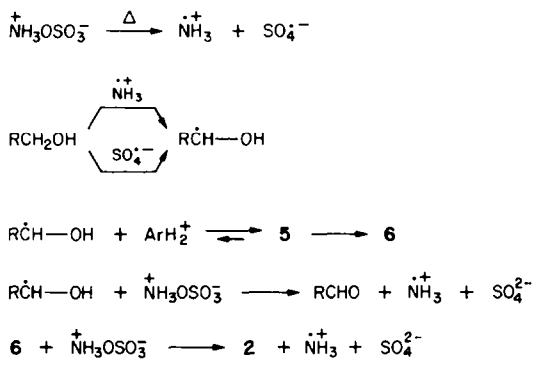
The nitrile is formed by subsequent ionic reaction with HOSA of the aldehyde formed by oxidation of $R\dot{C}HOH$ radicals (Eq. 10).

$$RCHO + \overset{+}{N}H_3OSO_3^- \xrightarrow{-H_2O} RCH{=}NOSO_3H \rightarrow RCN + H_2SO_4 \quad (10)$$

Similar processes of HOSA and carbonyl compounds are well known,[3] and the example reported in



Scheme 1.



Scheme 2.

this work represents a new way to obtain in one-pot nitriles from the corresponding primary alcohols.

The previous considerations (high reversibility of addition and high oxidability) can be used to explain also the complete absence of addition products with $(CH_3)_2\dot{C}OH$ radicals.

EXPERIMENTAL

M.ps were determined on a Reichert Koffler and are uncorrected. Analytical gas liquid chromatographic analyses were performed with a Carlo Erba 4200 or a Dani 3600 equipped with flame ionization detectors. Use was made of 2 m columns packed with 10% OV 101 on Chromosorb W HP DMCS (80–100 mesh) and 10% Carbowax 20 M on Chromosorb W DMCS. Quantitative TLC analyses were performed by using a CAMAG TLC scanner at 280 nm (Hg lamp) on HPTLC (Merk). In all cases peak areas were determined with a Spectra Physics SP 4100 integrator as a mean of two independent experiments.

Materials. 4-Methylquinoline, 2,4-dimethylquinoline and 4-cyanopyridine were obtained from EGA, 2-methylquinoline from Backer, $FeSO_4 \cdot 7H_2O$, $Fe_2(SO_4)_3 \cdot nH_2O$ (20% Fe), butyrronitrile, pentanonitrile, methanol, ethanol and butanol were obtained from Carlo Erba. Methanol was distilled on Mg and stored on molecular sieves under N_2. HOSA (EGA) was used after iodometric titration (93–98%); it was stored under vacuum on P_2O_5.

The following products of hydroxyalkylation were isolated from the reaction mixtures and found identical to the one previously described: 2-hydroxymethyl-4-methylquinoline (m.p. 85°, lit.[11] 85°), 4-hydroxymethyl-2-methylquinoline (m.p. 147°, lit.[11] 146–7°), 2-hydroxymethyl-4-cyanopyridine (m.p. 94–95°), 2-hydroxyethyl-4-methylquinoline (m.p. 66–68°).

Homolytic decomposition of HOSA in methanol in the presence of heteroaromatic base. In a 25 ml flask, equipped with magnetic stirrer were introduced in the order the heteroaromatic base (4 mmol), methanol, water (in the amounts reported in Table 1), conc. H_2SO_4 (0.20 ml, 4 mmol) and eventually $FeSO_4 \cdot 7H_2O$ or other materials (in the amounts reported in Table 1). The soln was flushed with N_2 for 5 min and poured in a thermostatic bath for 10 min. Then HOSA (in the amount reported in Table 1) was added. Gas evolution was observed and the temp increase (2–10°). The reaction was generally run for 4 hr, then transferred in a separatory funnel and washed with water (10 ml). Sodium citrate (0.3 g) was added and the soln basified at pH = 10 with 30% NH_3 soln, then extracted with CH_2Cl_2 (4 × 10 ml). The combined extracts were washed with water (10 ml) and dried. The solution, made up to 50 ml, was quantitatively analyzed on HPTLC plates (100 nl deposition) by using calibration curves for starting and final product obtained from five solutions of the same volume and containing different amounts of the two products.

HOSA decomposition in ethanol. A procedure similar to one reported for methanol was used with ethanol by using the reagents in the amounts reported in Table 2. The analyses were carried out, on the final solution obtained as above, by GLC after addition of 2,4-dimethylquinoline and pentanonitrile as internal standards. The 2-hydroxyethyllepidine was determined on the OV 101 column (prog. 20°/min. from 160° to 250°), whereas the acetonitrile was determined on Carbowax 20 M (isotherm 70°). The results obtained are reported in Table 2.

HOSA decomposition in the presence of butanol. To a solution of n-butanol (0.36 g, 4 mmol) in water (6 ml) were added under stirring lepidine (0.57 g, 4 mmol), conc. H_2SO_4 (0.2 ml, 4 mmol) and $FeSO_4 \cdot 7H_2O$ (33 mg, 0.12 mmol). The solution was warmed at 80° and HOSA (0.49 g, 4 mmol) was added. The reaction was allowed to run for 2 hr, then cooled, basified at PH = 10 with NaOH 10% and extracted with CH_2Cl_2 (4 × 20 ml). Combined extracts were washed with water, dried, made up at 100 ml, after addition of known amounts of 2,4-dimethylquinoline and pentanonitrile. The analyses were carried out as described for reactions with ethanol. The following results were obtained: recovered lepidine 92%, 2-α-hydroxybutyllepidine 0.1%, n-butyrronitrile 30% based on HOSA. An analogous reaction without the base afforded n-butyrronitrile in 15% yield.

Hydroxymethylation of lepidine by HOSA in methanol in the presence of the couple Fe^{2+}/Fe^{3+}. A stock soln was made adding lepidine (2.8 ml, 21.2 mmol) to MeOH (32 ml) and water (14 ml) and then conc. H_2SO_4 (0.78 ml, 15.7 mmol) and $FeSO_4 \cdot 7H_2O$ (0.130 g, 0.47 mmol). The soln was flushed under N_2 for 10 min and thermostated at 20°. 12 ml of homogeneous soln were added to a thermostated (20°) flask containing weighted amounts of $Fe_2(SO_4)_3 \cdot nH_2O$ (Fig. 1) and water (6 ml). HOSA (0.5 g, 4 mmol) was added at last. The reaction was run for 4 hr. The work up was carried out as above.

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