Redox-chain Decomposition of Hydroxylamine-*O*-sulphonic Acid. A Novel General Source of Nucleophilic Radicals for the Functionalization of Heteroaromatic Bases

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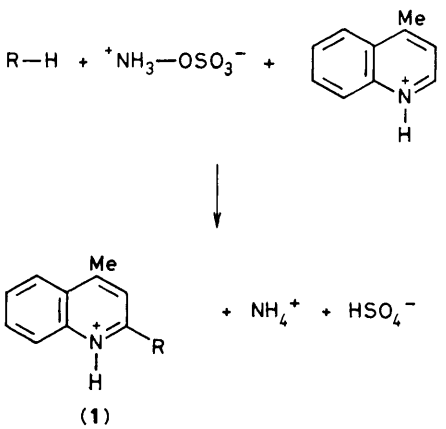
Protonated heteroaromatic bases react with formamide, *N,N*-dimethylformamide, cyclic ethers, and methanol in the presence of hydroxylamine-*O*-sulphonic acid and catalytic amounts of an iron(II) salt to afford selective substitution by a redox chain process.

The reaction of nucleophilic carbon-centred free-radicals with protonated heteroaromatic bases is one of the most significant substitution reactions of these substrates.[1] General free-radical sources for these substitutions involve the initial formation of an electrophilic radical, which does not attack the heteroaromatic bases but can react with suitable substrates to generate nucleophilic radicals.[1]

In this context we report a novel, simple, and general process of heteroaromatic substitution by iron(II)-catalysed decomposition of hydroxylamine-*O*-sulphonic acid (HSA) in the presence of hydrogen donor molecules (R–H) (Scheme 1). Table 1 summarizes results for the formation of compound (**1**) with 4-methylquinoline as representative heteroaromatic base (ArH) and formamide, *N,N*-dimethylformamide, cyclic ethers, and methanol as hydrogen donor (R–H). With all radicals the observed substitution with this substrate occurs selectively at position 2. No reaction was observed under the same conditions in the absence of Fe^{II} salt at 20 °C. At higher temperatures (80 °C) substitution was observed in the absence of Fe^{II} but in low yield. Other heteroaromatic bases afford analogous results.

The reaction has the features of a redox chain process since small amounts of Fe^{II} salt lead to an exothermic reaction with complete decomposition of HSA in a few minutes at room temperature (experiments with *N,N*-dimethylformamide and methanol). We suggest that our results are best rationalized by the one-electron redox chain of Scheme 2. With methanol, dioxane, and formamide only one radical is formed by hydrogen abstraction, the radicals (**2**), (**3**), and (**4**), respectively, which selectively attack position 2 of 4-methylquinoline.



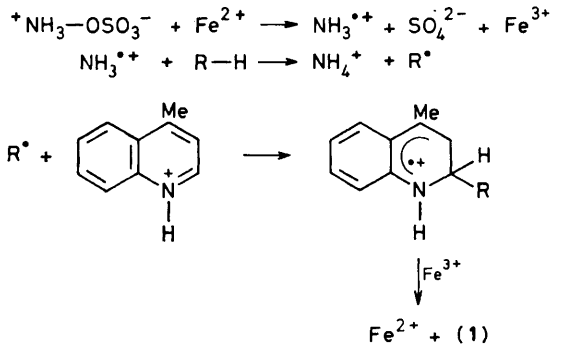
(**1**)

Scheme 1

Table 1. Homolytic substitution at position 2 of protonated 4-methylquinoline by nucleophilic radicals generated by iron(II)-catalysed decomposition of HSA in the presence of hydrogen-donor solvents R–H.[a]

R–H	% Base conversion	Radical	% Yield[b]
MeOH[c,d]	53	(2)	90
MeOH[d,e]	85	(2)	93
MeOH[c,d]	1	(2)	—
Dioxane[c]	65	(4)	92
Dioxane[e]	93	(4)	96
Dioxane[c]	6	(4)	95
THF[c,f,g]	25	(5)	84
		(6)	12
THF[c,g,h]	6	(5)	32
		(6)	63
$HCONH_2$[c]	50	(3)	84
$HCONMe_2$[c,d]	40	(7)	8
		(8)	84
$HCONMe_2$[d,e]	70	(7)	6
		(8)	80

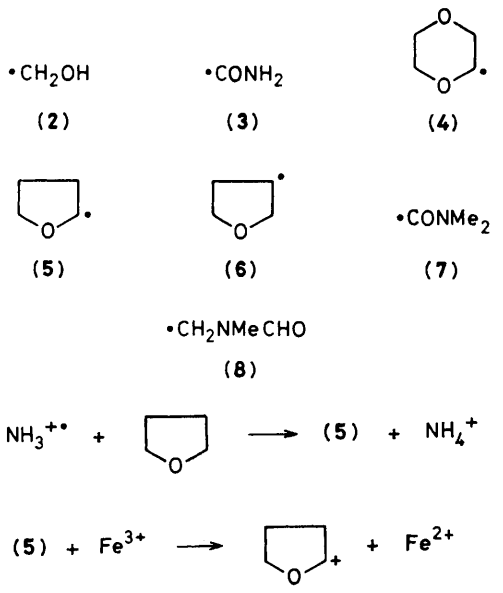
[a] 3% Aqueous $FeSO_4$ at 20 °C for 4 h. [b] Based on converted base. [c] 4-Methylquinoline:HSA 1:1. [d] Reaction for 15 min. [e] 4-Methylquinoline:HSA 1:3. [f] THF = tetrahydrofuran. [g] At 80 °C. [h] In the presence of Fe^{III} (3 mol. equiv.).



Scheme 2

With tetrahydrofuran the hydrogen abstraction mostly occurs at the α-position to give the radical (**5**), but it occurs to a significant extent at the β-position also with formation of the radical (**6**).

Previous e.s.r. studies[2] had concluded that $NH_3^{\bullet+}$ radicals generated from $^+NH_3OH$ and Ti^{III} afford only the radical (**5**). Both radicals (**5**) and (**6**) selectively substitute position 2 of 4-methylquinoline, but the ratios of products obtained are strongly affected by the amounts of Fe^{III} salt in solution, which is able to oxidize the radical (**5**),[3] but not the radical (**6**), by a redox chain (Scheme 3) parallel to that of Scheme 2. Thus on increasing the amount of Fe^{III} salt the overall yield



Scheme 3

decreases as does the extent of attack of the radical (**5**) relative to (**6**).

With *N,N*-dimethylformamide both the formyl and methyl hydrogen atoms may be abstracted giving the radicals (**7**) and (**8**), respectively, which substitute the 2-position of 4-methylquinoline. The attack of (**8**) strongly predominates over the attack of (**7**). Polar effects, bond strengths, and the different susceptibility to oxidation of the two radicals by the Fe^{III} salt all contribute to determining the ratio of attack reported in Table 1.

The easy availability of HSA, the good yields and selectivity, and the simple experimental conditions make this reaction attractive as a general method for functionalizing heteroaromatic bases. This work indicates also that HSA is readily involved in efficient free-radical redox chains and its homolytic reactivity is certainly wider than that reported in a recent review.[4]

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