

**N-HYDROXY-2-PYRIDINETHIONE: A MILD AND CONVENIENT
SOURCE OF HYDROXYL RADICALS**

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Abstract: N-Hydroxy-2-thiopyridone gives hydroxyl radicals on irradiation with visible light and these can be incorporated in useful radical chain processes involving hydrogen abstraction.

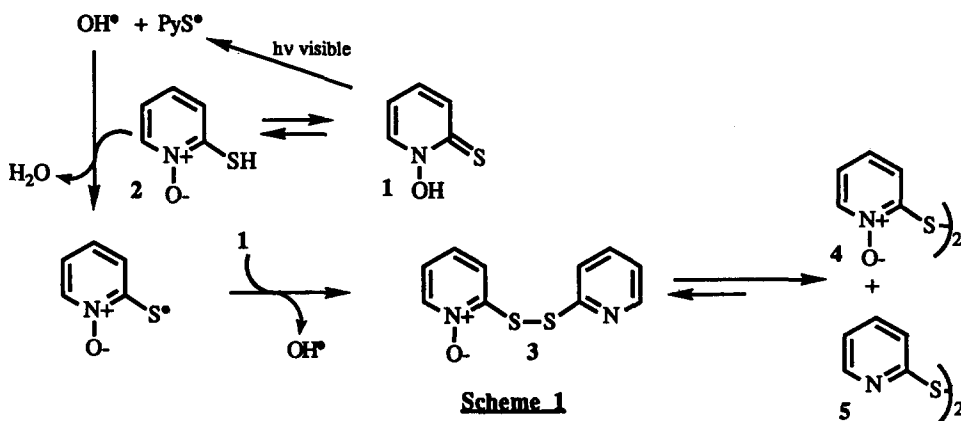
Following the pioneering work of Barton and collaborators, derivatives of N-hydroxy-2-pyridinethione **1** such as esters, carbamates, ethers, and carbonates have emerged as very valuable sources of carbon¹, nitrogen², or oxygen^{3,4} centered radicals. The process, usually triggered either thermally or by photolysis with visible light, has allowed a facile and high yielding access to a tremendous variety of functionalised molecules⁵.

However, the radical chemistry of the simplest member of the family, i.e. **1**, has hardly been explored. Compound **1** is a nice white crystalline solid, in contrast to its derivatives which are yellow coloured substances; it is produced industrially on a large scale since its zinc and sodium salts are widely used as anti dandruff, antifungal, and antimicrobial additives in a variety of commercial formulations⁶. Recently, we noticed fortuitously that, when exposed for few minutes to sunlight, compound **1** turned into an orange-yellow colour. This observation suggested, by analogy with the radical chemistry of its derivatives, the possibility of using **1** as a source of hydroxyl radical on irradiation with visible light. In this Letter, we wish to report preliminary results which indicate that this is indeed the case.

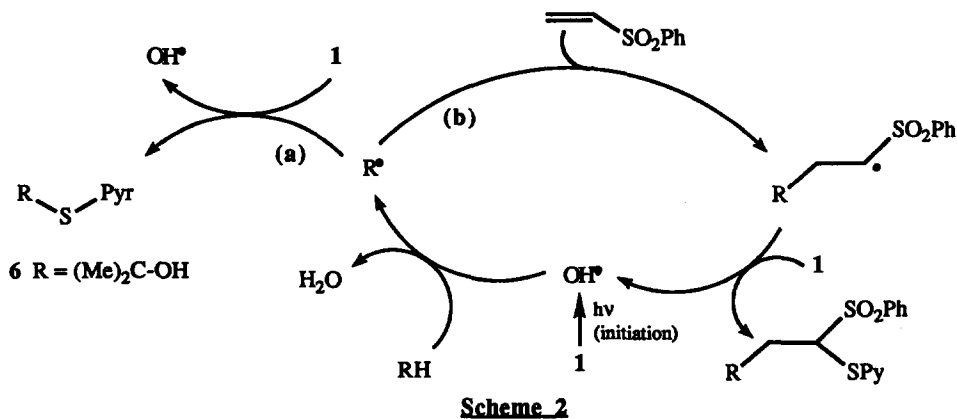
Irradiation of a solution of **1** in benzene (500 W tungsten lamp) for 3 hours afforded a mixture of dipyrityl disulphide **5** (30%), and its oxidised derivatives **3** (48%) and **4** (18%). Monitoring of the reaction by thin layer chromatography indicated that the rather unstable disulphide **3** is formed first and then slowly undergoes disproportionation to give **4** and **5**, a process typical of unsymmetrical disulphides^{7b}. Consequently, the relative yields of **3**, **4**, and **5** varied considerably from one experiment to another. A plausible explanation for the photochemical behaviour of **1**, involving the intermediacy of hydroxyl radicals, is displayed in scheme 1.

A characteristic reaction of hydroxyl and alkoxy radicals in general is hydrogen abstraction⁸. Carbon-hydrogen bonds weakened by a heteroatom as found in alcohols, ethers, acetals, amines etc... are particularly prone to abstraction by reactive oxygen centered radicals⁹. As therefore

expected, irradiation with visible light of a solution of 1 in refluxing isopropanol for 2 hrs produced acetone which was isolated and characterised as its DNP derivative (50% based on 1). Thus, the dimethyl hydroxymethyl radical formed by abstraction of the tertiary hydrogen from isopropanol adds onto the thiocarbonyl group of 1 to give after fragmentation hemi-thioetheral 6 (which collapses into acetone) and another hydroxyl radical thereby propagating the chain. This corresponds to pathway (a) in the manifold pictured in scheme 2.



In a synthetically more useful modification, the intermediate nucleophilic carbon radical may be captured by an electrophilic olefin such as phenyl vinyl sulphone as shown in the reaction sequence outlined in scheme 2, pathway (b). The results for isopropanol are collected in the Table (entries 1-5).



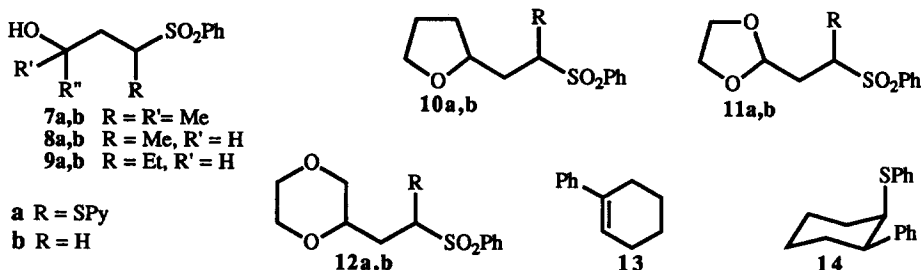
The expected product, 7a, was accompanied by variable amounts of 7b, which results from abstraction by the transient α -phenylsulphonyl radical of either the tertiary hydrogen CH_2OH in isopropanol, used in large excess both as reactant and solvent, or the thiol hydrogen in tautomer 2. The best overall yield was obtained using 3 mmol. of phenyl vinyl sulphone in 10 ml of i-PROH (entry 2). The selectivity, measured by the ratio 7a/7b, can be adjusted by varying the reaction conditions (compare entries 1-5).

Table. Photolytic decomposition of **1** in various alcohols, ethers, and acetals, in the presence of phenyl vinyl sulphone.

Entry	Substrate (as solvent)	Volume (ml)	1 (mmol.)	Phenyl vinyl sulphone (mmol)	Temperature	Products (yield %) ^a
1	Isopropanol	10	1 ^b	3	reflux	7a (28); 7b (38)
2	Isopropanol	10	1	3	reflux	7a (52); 7b (29)
3	Isopropanol	4	1	3	reflux	7a (24); 7b (9)
4	Isopropanol	10	1.5	1	reflux	7a (42); 7b (12)
5	Isopropanol	10	3	1	reflux	7a (50); 7b (10)
6	Methanol	10	1	3	reflux	8a (17); 8b (8.5)
7	Ethanol	10	1	3	reflux	9a (22); 9b (5<)
8	THF	10	1	3	reflux	10a (46); 10b (19)
9	THF	10	1	3	20°C	10a (13); 10b (0)
10	1,3-dioxolane	10	1	3	reflux	11a (31); 11b (37)
11	1,3-dioxolane	10	1	3	20°C	11a (38); 11b (0)
12	1,4-dioxane	10	1	3	reflux	12a (64); 12b (13)

a) Yields are based on **1**, except for entries 4 and 5 where yields are based on phenyl vinyl sulphone. b) **1** was added in small portions to the irradiated, refluxing solution.

Other substrates containing easily removable hydrogens such as methanol, ethanol, tetrahydrofuran, 1,3-dioxolane, and 1,4-dioxane, were also examined (Table, entries 6-12). Combined yields are moderate for simple alcohols (entries 6 and 7) but increase in the case of ethers (c.a. 65-75%, entries 8, 10, and 12). Even if the overall yield decreases, the influence of lowering the temperature on the product distribution (entries 9 and 11) is particularly worthy of note and follows the intrinsic propensity of the intermediate sulphone substituted "electrophilic" radical to attack the thiocarbonyl group of **1** rather than the C-H-O carbon-hydrogen bond.



The possibility of using OH[•] radicals generated in this manner as a catalytic initiator in radical chain reactions was also briefly studied. The well-known radical addition of thiols onto olefins¹⁰ was chosen as a test case. Indeed irradiation with visible light for 6 hrs at room temperature, under anaerobic conditions, of a solution of 1-phenyl-cyclohexene **13** (2 mmol.) and thiophenol (4 mmol.) in tetrahydrofuran (1 ml) containing 0.2 equivalent of **1** afforded adduct **14** (53% based on **1**, not optimised), together with recovered starting material (43%).

Relatively few methods are convenient for generating hydroxyl radicals. The most useful are metal catalysed (especially iron) decomposition of hydrogen peroxide and organic hydroperoxides (the well-documented Fenton reaction)^{11,12}. Photolysis or radiolysis of water have also been used¹³ but these are rather harsh conditions. This present method offers the advantages of ready availability, ease of operation, and mildness of conditions. Moreover, unlike previous processes, the

hydroxyl radicals are produced in a chain mechanism. The system therefore is much easier to control since the steady state concentration of radicals remains small and unwanted radical-radical interactions are minimised.

In addition to the various possible synthetic applications, this method can also serve as a tool for studying many of the crucially important biological processes, whether beneficial (catabolism, oxidative transformations in particular) or deleterious (ageing, oncogenesis etc.), which appear to involve hydroxyl radicals¹⁴.

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