

Advances in the chemistry of stable nitroxides

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Abstract - The paper discusses syntheses of new nitroxides by structure modifications of known carbocyclic and heterocyclic nitroxides and their diamagnetic precursors, as well as syntheses of nitroxides with a functional group in close proximity to the radical centre. It demonstrates a new route to pyrrolidine nitroxides. Much has been focused on 3-imidazoline and 3-imidazoline-3-oxide nitroxides owing to their stability to acids and oxidants, complexing ability and remarkable reactivity.

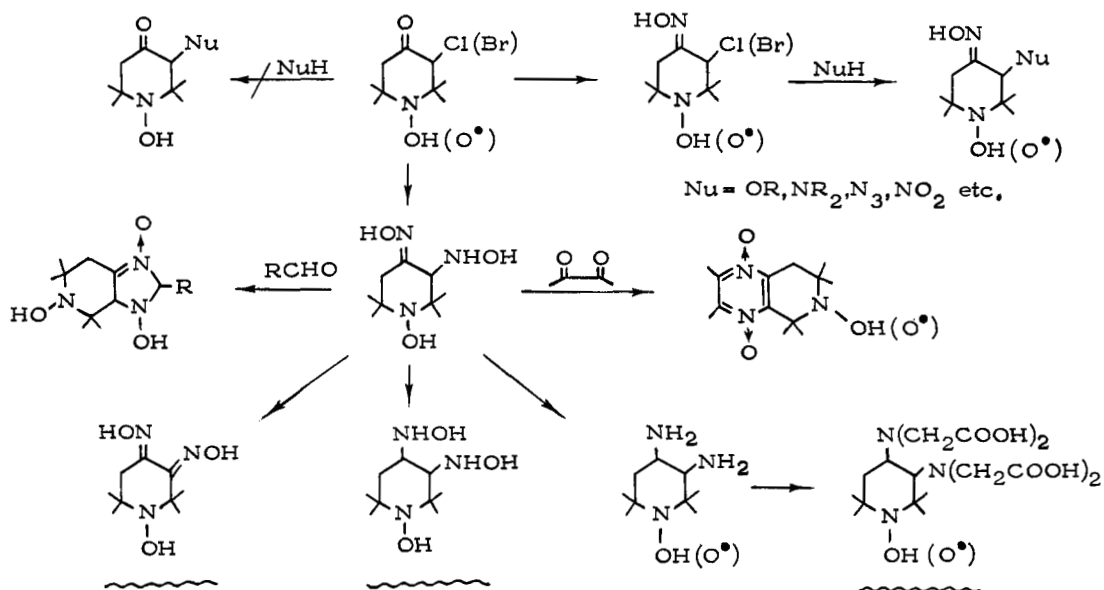
The progress in the chemistry of nitroxides is largely stimulated by expanding scientific and practical applications of these compounds. On the other hand, creation of new structural types gives rise to new applications of nitroxides. This paper presents compounds and methods of their synthesis realized during recent years and unsynthesized compounds whose synthesis may be outlined based on our current knowledge. Such compounds are underlined on the schemes by a wavy line. And if such conceivable structures are of interest for anybody, efforts may be taken to realize them.

The purpose of the paper is to stimulate imagination of all specialists engaged in application of nitroxides and nitrones as spin labels, spin probes and traps, as well as of paramagnetic and ferromagnetic substances. Any ideas and structures should be discussed and taken into account, including the most fantastic ones. Such discussions may prove useful to solve not only some particular problems but also prospective ones.

The chemistry of α, β -unsaturated aldehydes and ketones, dienes, etc. synthesized from pyrrolidine and piperidine derivatives has been recently developed by Hideg (ref. 1) and Shapiro (ref. 2). It is worthwhile to note a rather useful condensation reaction of 1-hydroxytriacetoneamine with thiophene in the presence of sulphuric acid, giving better yields than triacetoneamine itself and affording spin-labelled compounds (ref. 3). Here we shall consider the works dealing with functionalization of the piperidone ring, which were not covered by the last review by Keana (ref. 4) and articles by Hideg and Shapiro.

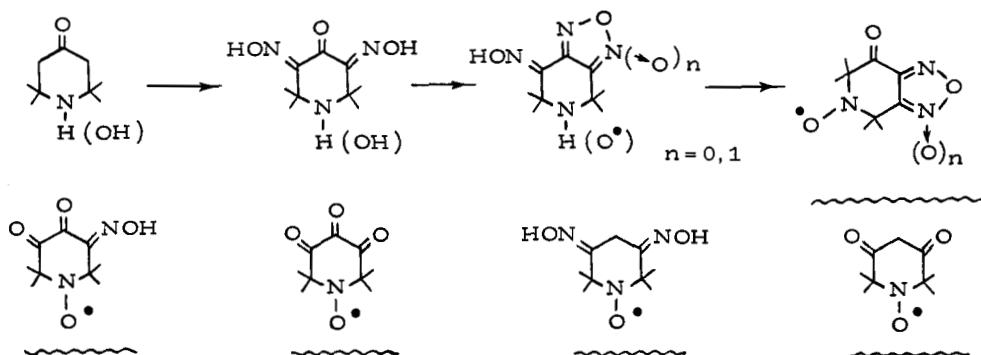
The nucleophilic substitutions of halogen in 3-halogen-substituted triace-

toneamine, its hydroxyderivative and radical were unsuccessful. However for oximes of these halogenketones, the nucleophilic substitution proceeded quite readily because in this case the reaction follows the elimination-addition scheme. These reactions gave amino, hydroxy and nitrooximes (ref. 5).



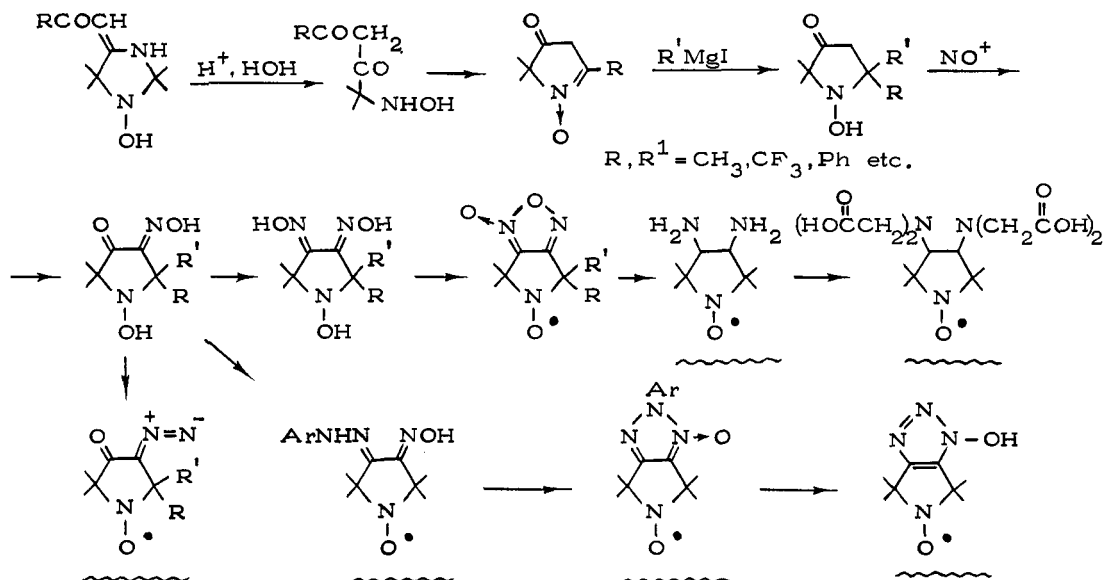
In continuation of these studies, 1,2-hydroxylamino-oxime was synthesized (ref. 6). Its condensation with α -diacetyl led to pyrazine N,N-dioxide which was oxidized to give a nitroxide. 1,2-Hydroxylamino-oxime may be used as the starting compound for the synthesis of dioxime, dihydroxylamine, diamine, nitrones, heterocyclic compounds, etc. (ref. 7).

The ability to synthesize functional derivatives of triacetoneamine has been demonstrated on the reactions and transformations of the its dihydroxyimino-derivate (ref. 8) to furoxane, furazane, ketones, etc..



The synthesis of interesting 3-pyrrolidone nitroxide is multistep and radical environment is just the same as in starting triacetoneamine. The use of imidazolidine enaminketone recyclization to synthesize 3-pyrrolidone derivatives afforded the compounds containing, instead of one or two methyl groups phenyl, trifluoromethyl, tert-butyl, etc. (ref. 9). For metal complexes of 3,4-dihydroxyiminopyrrolidine nitroxide, conductance of the system considerably grows upon substitution of methyl by trifluorinemethyl

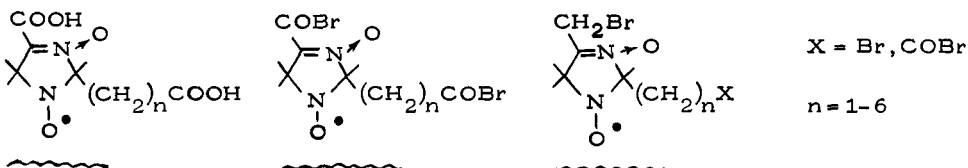
group. Easy formation of the furoxane ring encourages attempts to form the triazole ring. It is useful to find out the possibility of preparation triazoketone, diamine and diaminotetraacetic acid.

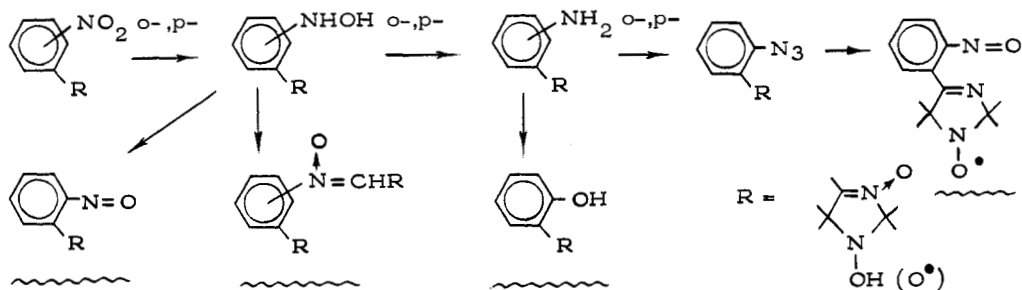


Considering heterocyclic nitroxides we shall discuss 3-imidazoline and 3-imidazoline-3-oxide nitroxides as they have a number of peculiarities as compared to nitroxides of other types (ref. 9, 10).

Recently it has been found that in the ESR spectrum of 3-imidazoline and imidazolidine nitroxides consisting of three peaks, the right-hand component in acid media is split into two peaks due to a slow exchange between the free and protonated 3-imidazoline and imidazolidine nitroxides. The same function is performed by the hfi constants. Evidently, labelling of some molecules with labels containing imidazoline fragment allows pH measurements for various cells and tissues (ref. 10). In this connection a question arises if the ESR spectrum will similarly react to coordination of the nitrogen in 3 position with metal ions and Lewis acids.

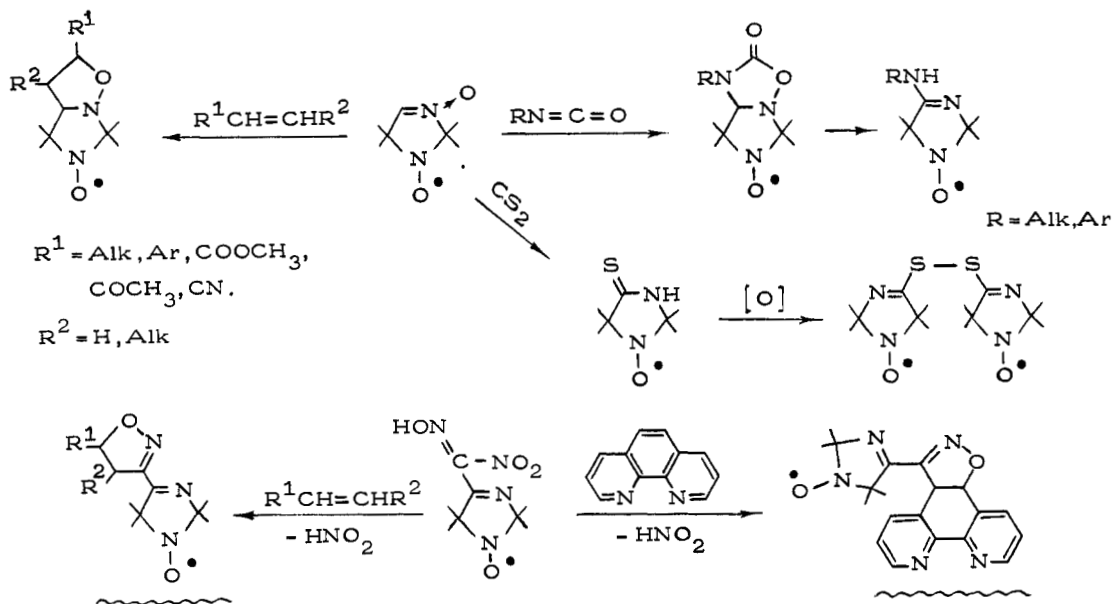
Due to the stability of 3-imidazoline-3-oxides nitroxides and their precursors against halogens, a wide variety of alkylating and acylating spin labels may be obtained with different substituents (ref. 9), lipophilities and mutual position of one or two functional groups with respect to the radical centre. Due to their stability to acids the nitration reaction has been carried out. The nitro-derivatives were used as the starting compounds for the synthesis of hydroxylamines, anilines, azo-derivatives and azide. One can expect that it would be possible to synthesize nitrones and nitroso derivatives from them.





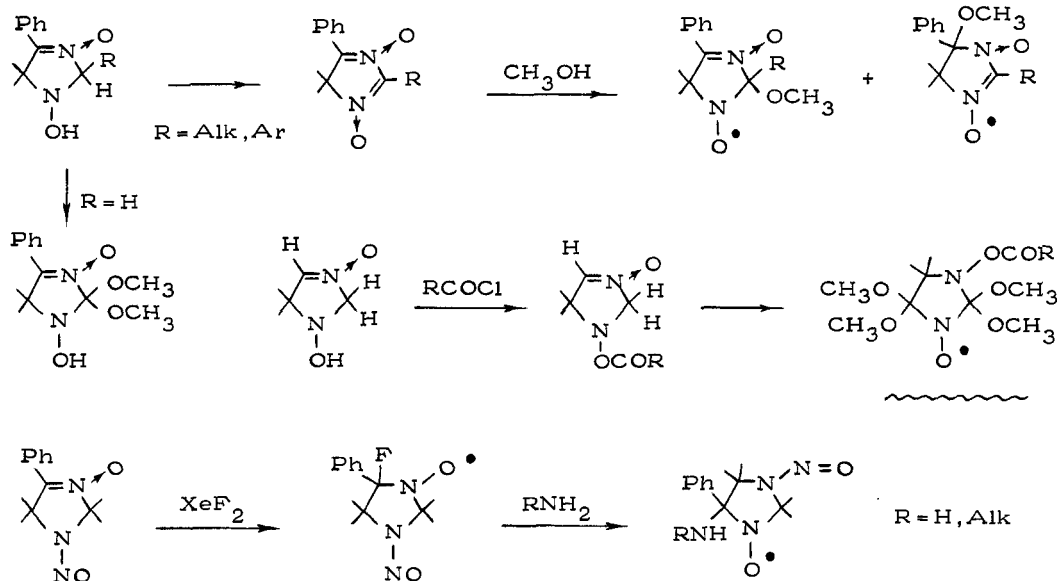
1,3-Dipolar addition of 3-imidazoline-3-oxide unsubstituted in the 4-position to compounds containing multiple bonds, including polymers, gives an adduct with a rigid cycle structure. In this case the radical mobility, which shows itself in the ESR spectrum, represents mobility of the whole molecule, contrary to the cases when a radical is attached to a molecule by an ordinary bond. The reaction of isocyanates with this aldonitrone affords amidines, whereas with carbon disulfide it gives sulphur containing derivatives (ref. 9).

Formation of cycloadducts is observed in the reaction of nitronitrosate imidazoline nitroxide (ref. 9) with compounds containing multiple bond, including those unreactive towards the afore mentioned aldonitrone. Due to this, the nitroxyl fragment might be introduced into oleic acid, etc..



As for nitroxides with functional groups instead of alkyls as the radical centre environment, the reaction of oxidative substitution at position 2 of 1-hydroxy-3-imidazoline-3-oxide has been found. Oxidation of the compound with lead dioxide in acetone or benzene led to 4H-imidazole-1,3-dioxide and in methanol to a mixture of nitroxide and nitronitroxide containing the methoxy group at α -carbon. With starting material unsubstituted in the 2-position the end product is 2,2-dimethoxy derivatives (ref. 9). These results are encouraging for the possibility of synthesizing nitroxides with four alkoxy groups.

Recently a reaction in close proximity to the nitroxide group has been realized. The interaction of 1-nitroso-3-imidazoline-3-oxide with xenon difluoride led to fluorine addition and formation of stable radical. The reaction of this radical with ammonia or amines resulted in fluorine substitution and formation of the amino-derivatives (ref. 11).



Thus, as shown by this report, the chemical possibilities of nitroxide modification are truly unlimited.

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