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SYNTHESIS OF STABLE NITROXIDES WITH AMINO GROUPS AND FLUORINE ATOMS AT α-CARBON OF THE RADICAL CENTRE

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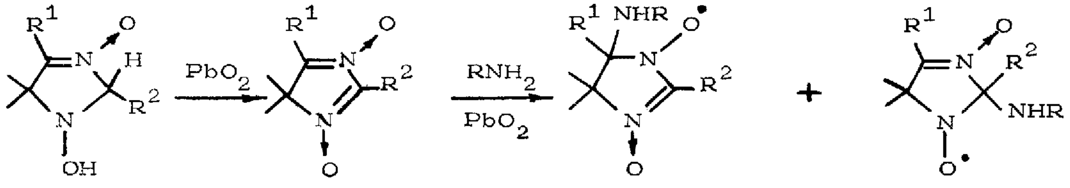
Summary: 2- and 3-Imidazoline nitroxides with amino groups in the position α to the radical centre are formed on oxidation of 4H-imidazole mono- and di-N-oxides in ethanolic solutions of NH_3 and CH_3NH_2. α-Fluorinated imidazolidine nitroxides have been obtained from 3-imidazoline-3-oxide derivatives by treatment with XeF_2 in CH_2Cl_2. Nucleophilic substitution of the fluorine atom resulted in formation of aminoimidazolidine nitroxides.

Oxidation of 4H-imidazole mono- and di-N-oxides with lead dioxide in alcohol has earlier been shown to produce stable nitroxides — 2- and 3-imidazoline derivatives with alkoxy groups at the α-carbon atom (α-C) of the radical centre.[1] This approach has also been found useful for the synthesis of stable nitroxides from cyclic aldonitrones.[2] In the case of the radicals with α-alkoxy groups it has been shown that the nitroxyl environment different from the traditional tetraalkyl screening imparts new spectral and chemical properties to the radicals.[3,4] This approach has been extended here to the synthesis of stable nitroxides with amino groups in close proximity to the nitroxide site. There are no data on stable nitroxides with primary or secondary amino groups among the groups screening the radical centre. However, ESR evidence for the existence of such radicals in solution has been obtained.[3-5]

Oxidation of 1-hydroxy-5,5-dimethyl-3-imidazoline-3-oxides 1 with an excess of lead dioxide in an ethanolic ammonia solution [6] for 20-30 hours gave stable nitroxides 3 and 4 with an NH_2 group at the α-C. In this reaction, as well as in the oxidation in methanol, the ratio of products depends on the nature of substituents R^1 and R^2. The ESR spectra of the blue nitronyl nitroxides 3 [7] consist of a quintet ($a_N^1 \simeq a_N^3$) with the intensity ratio of 1:2:3:2:1.

The ESR spectra of the yellow or brown nitroxides 4 [8] consist of a triplet of triplets ($a_N^1 \gg a_N^{NH_2}$) with equal intensity of each component.



1 2 3 4, 6

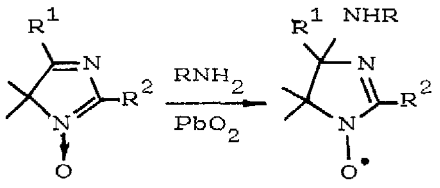
R= H (3, 4), CH_3 (6)

1			3			4			
	R^1	R^2	Yield,%	M.p.°C	a_N,G	Yield,%	M.p.°C	a_N^1,G	$a_N^{NH_2}$,G
a	Ph	Ph	90	38-40	7.54	-	-	-	-
b	Ph	m-Py	50	134-135	7.44	-	-	-	-
c	furyl-2	Ph	42	105-106	7.58	10	113-115	13.82	1.15
d	furyl-2	m-Py	30	141-142	7.58	10	170-172	13.79	1.00
e	5-CH_3-thienyl-2	Ph	-	-	-	20	171-173	13.73	1.29
f	5-CH_3-thienyl-2	m-Py	-	-	-	36	200-202	13.70	1.29

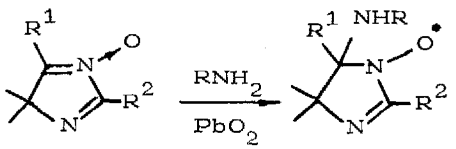
The g-factors of 3 and 4 are respectively 2.0067 and 2.0062 (in $CHCl_3$)

Nitronyl nitroxides 3 are more stable than nitroxides 4 and may be stored for months in the solid state and in solutions at room temperature. Nitroxides 4 are stable in the solid state during several days, but in solution are transformed in several hours to 4H-imidazole-3-oxides 5. Nitroxides 6 with the methylamino group at α-C formed by oxidation in saturated ethanolic CH_3NH_2 appeared to be more stable than nitroxides 4.[9]

Oxidation of 4H-imidazole N-oxides 5 and 7 under similar conditions produces imino nitroxides 8 and 9 in 90% yield. The ESR spectra of radicals 8 and 9 involve splittings by two nonequivalent nitrogen atoms N-1 and N-3: 8 a_N^1=8.80, a_N^3=4.30 G; 9 a_N^1=8.95, a_N^3=4.12 G. For these radicals, as for 3, there is no marked splitting by the amino nitrogen.

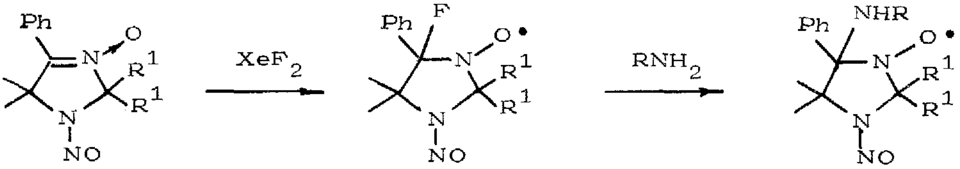


5 8



7 9

Compounds with the isolated phenylnitrone group — the 1-nitroso-4-phenyl-2,2,5,5-tetraalkyl-3-imidazoline-3-oxide derivatives 10 — do not lead under these conditions to nitroxides with α-amino groups (cf. ref.[2]). The reason for such different behaviour is that compounds 10 have higher oxidation potentials of the nitrone group than the 4H-imidazole N-oxide derivatives.[10] The use of xenon difluoride as a fluorinating agent led to stable nitroxides with fluorine atoms at α-C (11a,b), which may be stored in the solid state for several days.[11] The ESR spectra of the fluorinated radicals 11a,b show a doublet of triplets characteristic of the case with $a_N \ll a_F$: a_N=12.93, a_F= 45.38 G.



10a,b 11a,b 12a,b, 13a,b

R^1 = CH_3 (a), R^1+R^1 = $(CH_2)_5$ (b)

Interaction of nitroxides 11a,b with ammonia or methylamine in the ethanolic solutions gave the products of nucleophilic substitution of fluorine at α-C which led to the α-amino-substituted nitroxides 12 and 13.[12] The ESR spectra of nitroxides 12 and 13 present a triplet of triplets and are sensitive to the pH of the medium:[13, 14] for 12a a_N^1 = 15,50, $a_N^{NH_2}$=1.44 G at pH= 5.2; a_N^1 = 13.34, $a_N^{NH_3^+}$=3.37 G at pH=0.4. Nitroxides 12 and 13 are much more stable than nitroxides 4 and 6 and may be stored for months at room temperature.

All the nitroxides synthesised[15] have correct elemental analyses and have been characterised by ESR, UV, IR and Mass-spectra.

REFERENCES AND NOTES

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6. In contrast to methanol,[1] ethanol does not react with 2,5-disubstituted 4H-imidazole N-oxides 2, the initial products in the oxidation reactions.
7. 3a : IR (in KBr) cm^{-1}: $\nu\, NH_2$ 3410, 3340; UV (in ethanol) λ max, nm ($\lg\varepsilon$): 264 (4.14), 364 (4.08), 592 (2.80); Mass, M^+: 296.1389 (exp.), 296.1399 (calc.).
8. 4c : IR (in KBr) cm^{-1}: $\nu\, NH_2$ 3380, 3270; UV (in ethanol) λ max, nm ($\lg\varepsilon$): 301 (4.23); Mass, $(M-NH_2)^+$: 270.1011 (exp.), 270.1004 (calc.).
9. 6f : Yield 55%, M.p. 134°C (decomp.); ESR (in $CHCl_3$) G: $a_N^1 = 13.30$, $a_N^{NH} = 1.00$; IR (in KBr) cm^{-1}: $\nu\, NH$ 3280; UV (in ethanol) λmax, nm ($\lg\varepsilon$): 228 (4.07), 267 (3.86), 328 (4.17).
10. E_p vs. Ag/Ag^+, V: for 2, 5 and 7 1.0-1.3;[4] for 10 1.6-1.8.[2]
11. 11a : Yield 70%, M.p. 80-82°C (sublimation).
12. 12a : Yield 80%, M.p. 152-155°C; IR (in KBr) cm^{-1}: $\nu\, NH_2$ 3380, 3270.
    12b : Yield 70%, M.p. 145-147°C; IR (in KBr) cm^{-1}: $\nu\, NH_2$ 3380, 3320.
    13a : Yield 60%, M.p. 124-126°C; IR (in KBr) cm^{-1}: $\nu\, NH$ 3350.
    13b : Yield 55%, M.p. 117-119°C; IR (in CCl_4) cm^{-1}: $\nu\, NH$ 3370.
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15. All nitroxides were separated by column chromatography on silica gel with chloroform.

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