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A NEW SYNTHESIS OF (CHIRAL) NITROXIDES INVOLVING A SINGLE ELECTRON TRANSFER BETWEEN LITHIUM AMIDES AND MOLECULAR OXYGEN.

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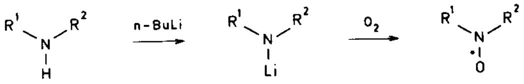
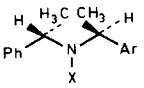
Abstract: Some (chiral) nitroxides have been synthesized by treatment of the corresponding lithium amides with molecular oxygen, which acts both as electron acceptor as well as oxygen atom donor.

Important methods of nitroxide formation start from the corresponding amines.[1] Examples are treatment of an amine with e.g. AIBN or di-t-butylperoxide in the presence of molecular oxygen (with intermediate formation of aminyl radicals)[2,3] or with hydrogen peroxides in the presence of tungstate, vanadate or molybdate (with intermediate formation of hydroxylamines).[1]

In the course of our work on chiral synthesis of ketones and esters by deprotonation/protonation using chiral lithium amides[4] we have found a new nitroxide synthesis. It was discovered that treatment of secondary amines with n-butyllithium followed by addition of molecular oxygen affords the corresponding nitroxides.[5]

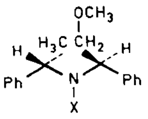


The procedure for 3a with THF as solvent is illustrated. Under an atmosphere of argon, 1.0 mmol (0.63 ml) of a 15% n-butyllithium solution in hexane was injected into a cooled (-40°C) solution of 1.0 mmol of 1a in 10 ml THF. After stirring for 0.5 hr. the argon was replaced by oxygen which turned the solution purple.[6] Upon warming the solution to room temperature the colour changed from purple to yellow and a strong ESR signal was observed[7] (Fig.) (the purple solution did not show an ESR signal!). By the same procedure we have synthesized nitroxides 3b - 3g.[8,9]



1 X = H
2 X = Li
3 X = O•

a Ar = phenyl
b Ar = o-methoxyphenyl
c Ar = m-methoxyphenyl
d Ar = 2-pyridyl



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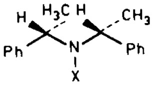

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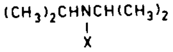
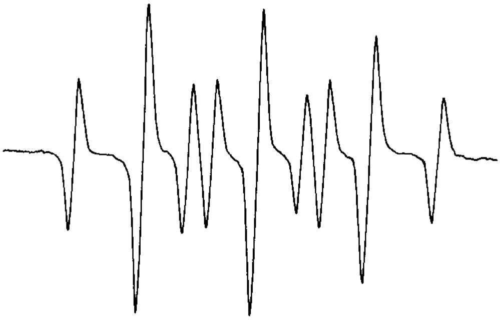


$\underset{X}{(CH_3)_2CHNCH(CH_3)_2}$

g



ESR-spectrum of 3a

The ESR-data of the nitroxides 3a - g are given in the Table

Table: ESR data of nitroxides 3a - g at 22°C

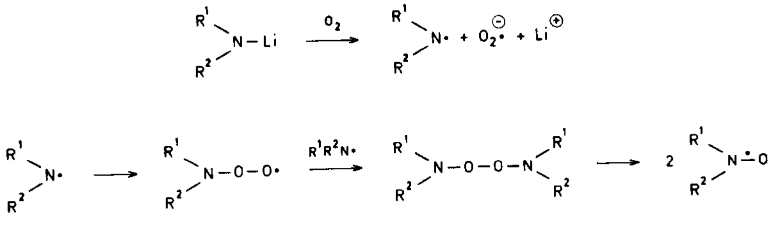
Nitroxide	Solvent	g	a^N (G)	a^H_β (G)
3a	THF	2.0060	14.9	9.0
3a	o-xylene	2.0062	14.9	9.0
3b	THF	2.0061	14.8	7.9;7.9
3c	THF	2.0061	14.9	8.6;8.6
3d	THF	2.0061	14.7	7.8;6.8
3e	THF	2.0061	14.8	9.7;5.5
3f	o-xylene	2.0062	14.6	5.9
3g	THF	2.0059	14.8	4.3

[a] Measured in a mixture of 3a and 3f (3a:3f = 1:4) at -25°C

The magnitude of the hyperfine splitting constants of the β-hydrogen (a^H_β) is a measure of the dihedral angle between the $2p_z$-orbital of nitrogen and the C-H bond. The values show that the structural changes have only a relatively small effect on the conformation of the nitroxides (the largest difference between the a^H_β values (9.5 G and 4.3 G resp.) corresponds with an difference in dihedral angle of only 13°, as calculated by the Heller-McConnell equation[10]).

In previous papers by de Boer et al[11] the ESR parameters of a nitroxide with the structural formula $[PhCH(CH_3)]_2N\dot{-}O$ were described (a^N = 15.1 G; a^H_β = 9.4 G). We conclude on basis of a comparison of these values with those of nitroxides 3a and 3f (Table) that the reported nitroxide has been a racemic mixture of (S,S) and (R,R) nitroxides (3a and enantiomer) rather than the meso-radical 3f. This points to a remarkable selectivity in the spin trapping reaction (addition of an 1-phenylethyl-radical to 1-phenylnitrosoethane) that was used for the formation of $[PhCH(CH_3)]_2N\dot{-}O$.[11]

We assume that the mechanism of formation of a nitroxide from the corresponding lithium amide includes two steps involving molecular oxygen.[12] In the first step oxygen presumably acts as electron acceptor from lithium amide, generating the aminyl radical.[13] The aminyl radical will subsequently react with a second molecule of oxygen forming a nitroxide dimer which then dissociates into the nitroxide.[14]



The electron transfer step in this mechanism finds support by the following observations in the literature: firstly, the reaction between LDA and benzophenon showed an ESR signal, pointing to an intermediate ketyl/aminyl radical pair rather than to a direct hydride transfer mechanism.[16] Secondly, the reaction between (sodium) benzophenone ketyl radical and molecular oxygen yielded benzophenon and (sodium) superoxide.[17] Summed up these two reactions (neglecting the difference in metal cation) yield the SET-step in our reaction scheme.

The above mentioned results underline the necessity of applying an inert atmosphere in experiments in which lithium amides are used.

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References and Notes

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3. To generate an amidyl radical also photolysis or thermolysis of tetrazenes or hydrazines is often used, see ref. 1a, page 572-573.
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   M.B. Eleveld and H. Hogeveen, to be published.
5. Although one of the first nitroxide radicals described (diphenyl nitroxide) was

obtained by reaction of diphenylamine with molecular oxygen in a toluene/alkaline alcohol solution, this method has not been applied afterwards, probably because of the reported restricted scope. R. Hoskins, J.Chem.Phys. 25, 788 (1956).

6. Except in the case of 1d and 1g, all other described amines gave a purple solution. With 1g the solution remained colourless after addition of n-butyllithium while 1d gave a dark reddish brown solution. Although this colour suggested that (partial) addition of n-butyllithium to the pyridine ring had occurred, see: G. Fraenkel and J.C. Cooper, Tetrahedron Lett., 1825 (1968), the NMR-spectrum of the product obtained after reprotonation showed this to be the case for <5%.
7. Sometimes a better ESR-spectrum was obtained by removing the dissolved oxygen by bubbling argon during 5 minutes through the solution.
8. The absolute configurations of the compounds were determined by either chemical correlation or X-ray analysis (F. van Bolhuis, Dept. of Structural Chemistry, Groningen). The absolute configuration of 1c has not yet been determined.
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