Reaction of 4*H*- *and* 2*H*-imidazole oxides with organolithium compounds, a novel route to stable nitroxyl radicals of the 2(3)-imidazoline series

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Reactions of 4*H*- and 2*H*-imidazole oxides with phenyl- and methyllithium followed by oxidation afford stable nitroxyl radicals — derivatives of 2- and 3-imidazolines including otherwise inaccessible sterically hindered radicals of the latter group. An unusual reaction, the formation of 2-azabutadiene derivatives after NO elimination in the dark, has been observed for pentaphenyl- and 5-methyltetraphenyl-3-imidazoline-1-oxyls.

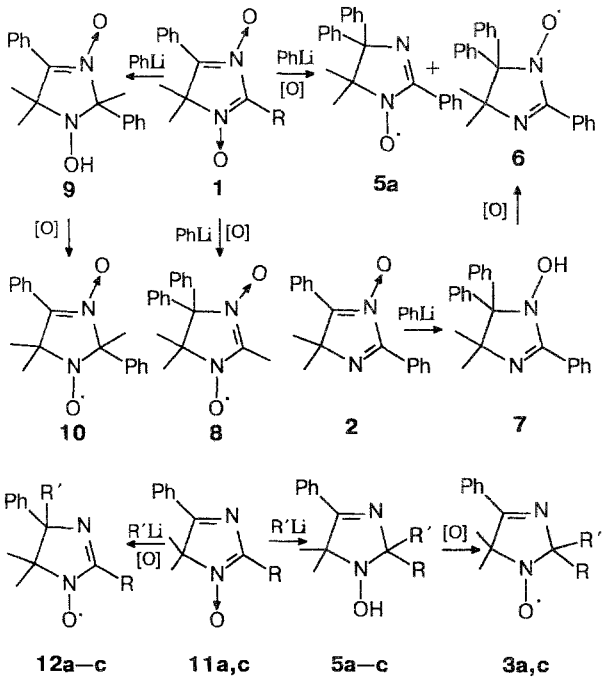
Key words: imidazole; imidazoline; nitroxyl radicals; nitrone; imine.

Previously we have demonstrated[1] that the reaction of 3-imidazoline 3-oxide derivatives existing in the cyclic tautomeric form, with organolithium compounds results exclusively in addition at the nitrone group of the heterocycle with the retention of the latter.[2] It is believed that 4*H*-imidazole dioxide (**1**), 4*H*-imidazole 1-oxide (**2**), 4*H*-imidazole 3-oxide (**3**), and 2*H*-imidazole 1-oxide (**4**) derivatives should react with organolithium compounds in a similar manner (Scheme 1). In this case the oxidation should afford otherwise inaccessible, stable nitroxyl radicals related to the 2- and 3-imidazoline series.

In the reaction of 4*H*-imidazole dioxide **1b** with excess phenyllithium the addition of only one mole of the reagent is observed; this addition occurs preferably at the phenylnitrone group and gives the nitronylnitroxyl radical **8** on subsequent oxidation. This reaction route obviously correlates with the ability of the methylnitrone group to be metallated thus preventing phenyllithium from binding at this position (see ref. 6). Quite unexpectedly, we found it possible to isolate the product of PhLi attachment to the methylnitrone group, 3-imidazoline 3-oxide **9** (see Scheme 1) from the reaction mixture, albeit in a small yield. Its structure was confirmed by its ^{13}C NMR spectrum. The latter shows, in particular, signals of the C(5) and C(2) atoms at 68.49 and 94.71 ppm, respectively, along with the signal of the carbon atom of the nitrone group at 141.91 ppm. Oxidation of compound **9** with MnO_2 affords a nitroxyl radical of the 3-imidazoline series, as evidenced by the similarity of IR and UV spectra of compounds **9** and **10** (*cf.* ref. 2).

Previously it was demonstrated[3] that when 4*H*-imidazole dioxide **1a** is subjected to excess phenyllithium attachment to both nitrone groups occurs. The reaction of **1a** with an equimolar amount of phenyllithium affords two isomeric iminonitroxyl radicals **5** and **6**. The position of the oxygen atom in the heterocycle was established by the independent synthesis of compound **6**, which was obtained in a high yield by the reaction of

Scheme 1



R = Ph (**a**), Me (**1b**), *o*-HOC_6H_4 (**3c, 5b,c, 12b,c**);
R′ = Ph (**11c, 12a,c**), Me (**12b**).

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 933—936, May, 1993.

4*H*-imidazole 1-oxide with excess of phenyllithium followed by oxidation of hydroxylamino derivative **7** (see Scheme 1). It should be pointed out that the addition of phenyllithium at the C=N bond of the phenylimino group does not occur (*cf.* ref. 5).

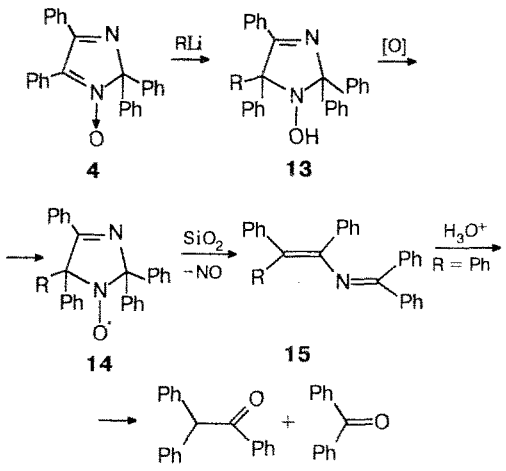
The reaction of 4*H*-imidazole 3-oxide **3a** with excess phenyllithium also results in the addition of only one mole of the reagent, preferably at the phenylnitrone group, to yield 1-hydroxy-3-imidazoline **11a**. The structure of **11a** was confirmed by its ^{13}C NMR spectrum, in which, in particular, the signal of the C(4) atom is observed at 174.22 ppm. The oxidation of compound **11a** readily affords the nitroxyl radical **12a** (see Scheme 1). Quite unexpectedly, it was found that the reaction of **3a** with phenyllithium affords the iminonitroxyl radical **5a** — the product of attachment to the phenylamino group, although in a small yield. The possibility of this reaction route is apparently related to the conjugation of the imino group with the nitrone fragment (*cf.* ref. 7). The reaction of compound **3b** with methyl- and phenyllithium proceeds in a similar manner — the major products of the reaction are nitroxyl radicals belonging to the 3-imidazoline series **12b,c**; the corresponding iminonitroxyl radicals **5b,c**, are also formed in small amounts. The former (**5b**) was obtained in the pure state, and the existence of the latter was deduced from the ESR spectrum of the mixture and was confirmed by thin-layer chromatography.

Thus, the reaction of 4*H*-imidazole 3-oxides with organolithium compounds is a novel, convenient method for the synthesis of nitroxyl radicals of the 3-imidazoline series. The method is similar to that used for obtaining nitroxyl radicals derived from pyrrolidine.[8] This procedure makes it possible to introduce substituents at position 2 of the heterocycle which cannot be introduced during heterocycle construction. Compounds **12b,c**, which are of great interest as potential paramagnetic chelating agents,[9] are examples of such compounds.

It is possible to obtain even more sterically hindered nitroxyl radicals **14** of the 3-imidazoline series by the reaction of 2*H*-imidazole 1-oxide **4** with methyl- and phenyllithium with subsequent oxidation of the produced 1-hydroxyimidazolines **13** (Scheme 2).

It was also found that the quantitative transformation of radicals **14** to diamagnetic compounds **15** occurs during chromatography on silica gel. The elemental analysis data indicate that the empirical formulae of **15** and of the starting reactants differ from one another by one NO group. The ^{13}C NMR spectrum of compound **15** shows only signals of sp^2-carbon atoms which, along with the elemental analysis data, indicates that their structure is acyclic. Hydrolysis readily affords phenyldiphenylmethylketone and benzophenone. Based on our results we assigned to compounds **15** the structures of 4-*R*-1,1,3,4-tetraphenyl-2-azabutadienes — the products obtained by eliminating NO from the parent radical. Although the possibility of a photochemical mechanism for this nitroxyl radical reaction has been long

Scheme 2



R = Me (**a**); Ph (**b**).

recognized,[10] we are the first to observe the cleavage of nitrogen oxide on silica gel.

Experimental

IR spectra were recorded on a Specord M-80 spectrometer as KBr pellets and in CCl_4 solution (5 %). UV spectra were taken on a Specord UV Vis instrument in an ethanol solution. The ^1H and ^{13}C NMR spectra were obtained in the pulse mode on a Bruker AC-2000 spectrometer at 300 K in $CDCl_3$ and DMSO-d_6 (5 %) solutions. All chemical shifts were determined relative to the solvent signal. Paramagnetic characteristics of the synthesized compounds were determined on a Minsk 12M EPR spectrometer. Compounds **1a**, **1b**, **2**, **4** were obtained according to the procedures described in refs. 1, 11, 12, 13, respectively. Characteristics of the synthesized compounds are given in Table 1, ^{13}C NMR spectra — in Table 2. Reactions with organolithium compounds were performed under an atmosphere of argon.

5,5-Dimethyl-2,4,4-triphenyl-2-imidazoline-1-oxyl (5a) and 4,4-dimethyl-2,5,5-triphenyl-2-imidazoline-1-oxyl (6). A solution of PhLi obtained from bromobenzene (0.32 mL, 3 mmol) and lithium (0.04 g, 6 mmol) in 10 mL of dry ether was added dropwise to a stirred solution of imidazole **1a** (0.58 g, 2 mmol) in 10 mL of dry THF. The stirring was continued for 15 min, then water (20 mL) was added, the organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$, and the drying agent was filtered off, MnO_2 (2 g) was added to the solution, and the solution was stirred for 30 min at 20 °C. The excess oxidant was filtered off, the solution was concentrated, and a mixture of compounds **5a** and **6** was separated by column chromatography on silica gel (elution with 1:1 hexane—chloroform). The first colored zone contained compound **5**, the second one — compound **6**.

1-Hydroxy-4,4-dimethyl-2,5,5-triphenyl-2-imidazoline (7). Imidazole **2** (0.79 g, 3 mmol) was added in portions to a stirred solution of phenyllithium obtained from PhBr (1.6 mL, 15 mmol) and lithium (0.21g, 3 mmol) in 30 mL of dry ether.

Table 1. Characteristics of compounds synthesized

Compound	Yield (%)	M.p.[a] /°C	IR spectrum (KBr), ν/cm^{-1} (C=C, C=N)	UV spectrum, λ_{max}/nm (log ε)	Found / Calculated (%) C	H	N	Molecular formula
5a	10	132—134	1545, 1560	237 (4.36), 309 (3.74), 455 (2.90)	79.9 / 81.0	6.1 / 6.2	8.1 / 8.2	$C_{23}H_{21}N_2O$
5b	5	112—114	1545, 1570, 1580, 1615	244 (4.0), 273 (3.72), 302 (3.62), 485 (2.84)	73.2 / 73.2	6.5 / 6.4	9.2 / 9.5	$C_{18}H_{19}N_2O_2$
6	10	167—169	1560, 1605	233 (4.44), 308 (3.58), 450 (2.78)	81.2 / 81.0	6.5 / 6.2	8.3 / 8.2	$C_{23}H_{21}N_2O$
7	100	218—219	1510, 1565, 1595, 1615	234 (4.30), 346 (2.90)	80.5 / 80.8	6.7 / 6.4	8.0 / 8.2	$C_{23}H_{22}N_2O$
9	15	220—223	1545, 1570, 1595	292 (4.10)	73.3 / 73.0	7.1 / 6.8	9.3 / 9.5	$C_{18}H_{20}N_2O_2$
10	95	110—112	1525, 1565	289 (4.03)	73.0 / 73.2	6.5 / 6.4	9.3 / 9.5	$C_{18}H_{19}N_2O_2$
11a	80	172—174	1570, 1600; 3560 (OH)[b]	243 (4.18)	80.4 / 80.7	6.6 / 6.4	8.0 / 8.2	$C_{23}H_{22}N_2O$
11c	95	144—146	1570, 1575, 1610; 3580 (OH)[b]	250 (4.04)	77.1 / 77.1	6.3 / 6.1	7.6 / 7.8	$C_{23}H_{22}N_2O_2$
12a	95	137—139	1565, 1605	253 (4.33)	81.1 / 80.9	6.4 / 6.2	8.2 / 8.2	$C_{23}H_{21}N_2O$
12b	60	Oil	1570, 1605, 1640; 3100—3400 (OH)[b]	250 (4.33)	73.0 / 73.2	6.6 / 6.4	9.2 / 9.5	$C_{18}H_{19}N_2O_2$
12c	80	140—142	1570, 1600; 3100—3400 (OH)[b]	253 (4.29)	77.5 / 77.4	6.1 / 5.9	7.9 / 7.9	$C_{23}H_{21}N_2O_2$
13a	90	159—161	1565, 1605; 3510 (OH)[b]	247 (4.24)	83.2 / 83.4	6.1 / 5.9	6.9 / 6.9	$C_{28}H_{24}N_2O$
13b	90	170—172	1565, 1600	248 (4.20)	84.7 / 84.9	5.7 / 5.6	5.8 / 6.0	$C_{33}H_{26}N_2O$
14b	90	165—167	1565, 1600	248 (4.22)	85.0 / 85.2	5.3 / 5.4	5.8 / 6.0	$C_{33}H_{25}N_2O$
15a	95	Oil	1570, 1595, 1620[b]	253 (4.40), 360 (2.90)	89.8 / 90.1	6.3 / 6.2	3.6 / 3.8	$C_{28}H_{23}N$
15b	100	189—190	1565, 1575, 1595, 1605	250 (4.34) 310sh (4.02), 385sh (3.48)	90.8 / 91.1	5.8 / 5.8	3.2 / 3.2	$C_{33}H_{25}N$

[a]Compounds **5a,b, 10, 12a** were purified by recrystallization from heptane; **6, 7, 11a,b, 13a,b** — from hexane—AcOEt; **9, 14b** — from ethanol, **12c, 15b** — from AcOEt. Compounds **12b, 15a** were isolated by chromatography. [b]The spectrum was recorded in CCl_4.

Table 2. ^{13}C NMR spectra (δ) of 3-imidazoline derivatives

Compound	Solvent	C(2)	C(4)	C(5)	Other signals
9	DMSO-d_6	94.71	141.91	68.49	21.90, 23.41, 26.31 (2,5,5-$(CH_3)_3$); 126.78—129.58 (m, 2,4-$(C_6H_5)_2$)
11a	DMSO-d_6	94.34	174.22	71.42	23.33 (5,5-$(CH_3)_2$); 126.44—144.46 (m, 2,2,4-$(C_6H_5)_3$)
13a	$CDCl_3$	96.29	171.66	*	16.6 (5-CH_3); 126.75—145.05 (m, 2,2,4,5-$(C_6H_5)_4$)
13b	$CDCl_3$	95.33	171.58	82.68	126.92—142.23 (m, 2,2,4,5,5-$(C_6H_5)_5$)

* The signal is overlapped with the signal of the solvent.

The stirring was continued for 15 min, then water (20 mL) was added, the precipitate of compound **7** was collected by filtration and washed with water. The organic layer of the filtrate was separated, and the aqueous layer was extracted with ether (3 × 20 mL). Organic extracts were combined, dried over $MgSO_4$, the solution was evaporated, the residue was washed with hexane, and the precipitate of compound **7** was collected by filtration. ^1H NMR ($CDCl_3$), δ: 0.87 (s, 6 H, 4,4-$(CH_3)_2$); 7.1 (m, 15 H, $(C_6H_5)_3$); 8.40 (br.s, 1 H, OH).

Iminonitroxyl radical **6** was obtained by oxidizing compound **7** (0.2 g) with MnO_2 (2 g) in $CHCl_3$. Excess oxidant was filtered off, and the solution was concentrated to give compound **6** in 95 % yield.

1-Hydroxy-2,4-diphenyl-2,5,5-trimethyl-3-imidazoline 3-oxide (9). The reaction of imidazole **1b** with phenyllithium was carried out in the manner described above. After the addition of water the organic layer was separated, and the aqueous layer was extracted with ether. Organic extracts were

combined, dried over $MgSO_4$, the solution was concentrated, the residue was washed with hexane, and the precipitate (**7**) was filtered. ^1H NMR (DMSO-d_6), δ: 1.23 (s, 3 H); 1.54 (s, 3 H); 1.85 (s, 3 H, 2,5,5-$(CH_3)_3$); 7.4 (m, 10 H, 2,4-$(C_6H_5)_2$); 8.44 (s, 1 H, OH).

3-Imidazoline 3-oxide **9** was oxidized to the nitroxyl radical **10** under the conditions described for compound **7**.

When the reaction of **1b** with phenyllithium was completed, $K_3Fe(CN)_6$ (5 g) was added to the aqueous solution and the solution was extracted with chloroform (5 × 30 mL). The extract was dried over $MgSO_4$, and the solution was concentrated to give compound **8**, which was purified by column chromatography on silica gel (elution with 1:1 ether—hexane), the yield 60 %, m.p. 108—110 °C (*cf.* ref. 2).

1-Hydroxy-5,5-dimethyl-2,2,4-triphenyl-3-imidazoline (11a) was obtained under conditions similar to those described for compound **7**. ^1H NMR (DMSO-d_6), δ: 1.30 (s, 6 H, 5,5-$(CH_3)_2$); 7.5 (m, 15 H, 2,2,4-$(C_6H_5)_3$).

5,5-Dimethyl-2,2,4-triphenyl-3-imidazoline-1-oxyl (12a) was obtained by oxidation of the mother liquor after recrystallization of **11a**. After the recrystallization of **12a** the iminonitroxyl radical **5a** was isolated from the mother liquor by column chromatography on silica gel (elution with 1:1 chloroform—hexane) in a 5 % yield.

1-Hydroxy-2-(2-hydroxyphenyl)-5,5-dimethyl-2,4-diphenyl-3-imidazoline (11c) was prepared using the same procedure as in the synthesis of **7**, and nitroxyl radical **12c** was obtained by oxidation of **11c** with MnO_2 as described above, and was purified by column chromatography on silica gel (elution with 1:1 chloroform—hexane). In the course of the chromatography imininitroxyl radical **5c** completely decomposed.

2-(2-Hydroxyphenyl)-2,5,5-trimethyl-4-phenyl-3-imidazoline-1-oxyl (12b). Imidazole **3b** (0.84 g, 3 mmol) was added portionwise to a stirred solution of phenyllithium obtained from methyl iodide (1.3 mL, 21 mmol) and lithium (0.29 g, 42 mmol) in 30 mL of dry ether. The stirring was continued for 2 h at 20 °C, 10 mL of water were added, and the aqueous solution was acidified with 10 % HCl to pH 4. The organic layer was separated, and the aqueous layer was extracted with ether. Organic layers were combined and dried over $MgSO_4$, which was then filtered off. MnO_2 (2 g) was added to the solution and the mixture was stirred for 20 min at 20 °C. Excess oxidant was filtered off, the solution was concentrated, and compound **12b** was purified by column chromatography on silica gel (elution with 1:1 chloroform—hexane). The aqueous solution was extracted with chloroform, and the extract was treated as described above. The residue was dissolved in ether and this solution was filtered through a pad of Al_2O_3 (see ref. 5). The filtrate was concentrated, the residue was washed with pentane (2 mL), and the precipitate of compound **5b** was collected by filtration.

1-Hydroxy-2,2,4,5,5-pentaphenyl-3-imidazoline (13b) and 1-hydroxy-5-methyl-2,2,4,5-tetraphenyl-3-imidazoline (13a) were obtained by reactions of phenyl- and methyllithium, respectively, with imidazole **4** under the conditions indicated for compound **7**. ^1H NMR for **13a** ($CDCl_3$), δ: 1.73(s, 3 H, 5 CH_3); 4.33 (br. s, 1H, OH); 7.4 (m, 20 H, $(C_6H_5)_4$). The oxidation of compounds **13** to nitroxyl radicals **14** was carried out with MnO_2 in $CHCl_3$ as described above. Compound **14a** could not be obtained in the chemically pure state. IR (KBr), ν/cm^{-1}: 1565, 1605 (C=C, C=N). UV (C_2H_5OH), λ_{max}/nm (log ε): 253 (4.34).

1,1,3,4,4-Pentaphenyl-2-azabutadien (15b). Compound **14b** (0.5 g) was subjected to column chromatography on silica gel (50 mL) (elution with 1:1 chloroform—hexane). The eluate was concentrated to yield **15b**. Under analogous conditions compound **15a** was obtained as a mixture of two isomers.

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Received June 11, 1992