Reaction of sterically hindered 1-hydroxy-3-imidazoline 3-oxides with phenyllithium

*V. A. Reznikov and L. B. Volodarsky**

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent'eva, 630090 Novosibirsk, Russian Federation. Fax:+7 (383) 235 4752

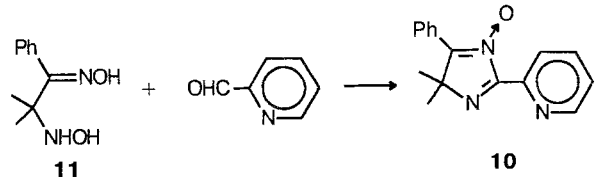
The reaction of 3-imidazoline 3-oxide derivatives with phenyllithium followed by oxidation affords nitroxyl radicals of the 2-imidazoline or 2-imidazoline 3-oxide series depending on the nature of the substituent in position 2 of the heterocycle.

Key words: imidazoline, nitroxyl radical, nitrone.

2,2,5,5-Tetrasubstituted 1-hydroxy-3-imidazoline 3-oxides (**1**) react with organomagnesium compounds with the opening of the heterocycle to form acyclic hydroxyaminooximes **2** (see Ref. 1). This is explained by the existence of a tautomeric equilibrium of compound **1** with its acyclic form **3**, so that the organomagnesium reagent adds at its nitrone group.[1] On the other hand, we have shown that the reaction of 4-phenyl-2,2,5,5-tetrasubstituted 3-imidazoline 3-oxides **1** with organolithium compounds involves exclusively the nitrone group of the cyclic form and affords the products of the addition at the C(4) atom (see Ref. 2). Compounds **1** can in fact exist in a solution as a mixture of two tautomers if one of the substituents in position 2 of imidazoline is an H atom.[3,4]

In the present work we studied the reaction pathways of sterically hindered **1** with PhLi as a function of the character of the substituent in position 2, which determines the possibility of a tautomeric equilibrium, and the possibility of using this reaction for preparing heterocyclic nitroxyl radicals.

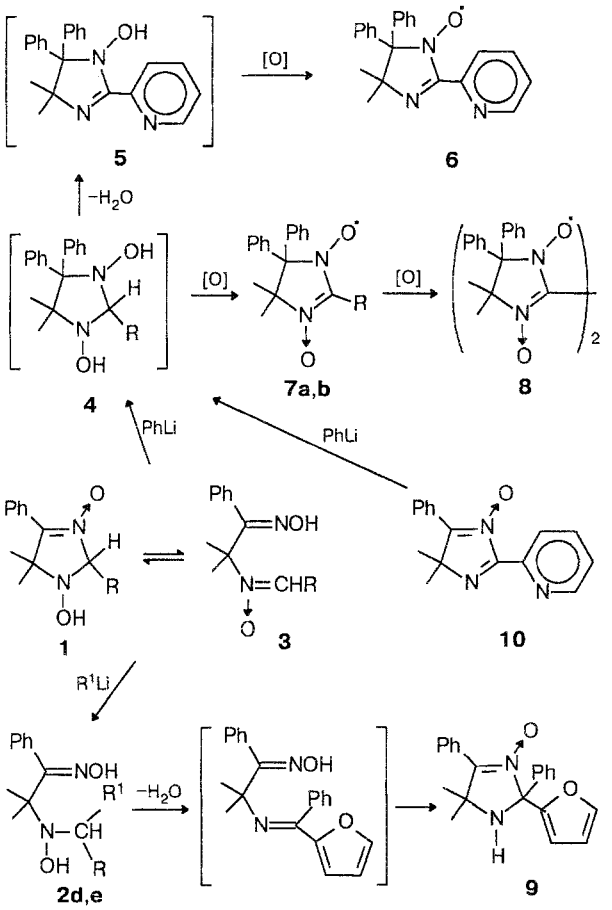
Compounds **1a,b,c** (see Scheme 1), which exist in solution as cyclic tautomers, react with PhLi to give the products of addition at the nitrone group of the heterocycle with the intermediate formation of dihydroxy derivatives **4** (*cf.* Ref. 2). In the case of compound **1c**, H_2O is eliminated to give intermediate **5**, whose subsequent oxidation affords the iminonitroxyl radical **6**. The position of the O atom in compound **6** was determined by its independent synthesis, *viz.*, by reacting 4*H*-imidazole 1-oxide **10** with PhLi and subsequent oxidation with MnO_2 (*cf.* Ref. 6). Compound **10** was prepared according to the following scheme:



11 **10**

Oxidation of imidazolidines **4a,b** does not involve elimination of H_2O; instead, nitronylnitroxyl radicals **7** are formed. Product **7a** cannot be isolated in the indi-

Scheme 1



1: R = H (**a**), CH_3 (**b**), 2-pyridyl (**c**), C_6H_5 (**d**), α-furyl (**e**)
2: R = R^1 = C_6H_5 (**d**); R = α-furyl, R^1 = C_6H_5 (**e**)

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vidual state due to its low stability, however, its subsequent oxidation with potassium ferricyanide in the presence of NaH as the base affords stable nitronylnitroxyl biradical **8** (Scheme 1) (*cf.* Ref. 5).

Compounds **1d,e**, exist predominantly in solution as the open-chain form **3**. In step 1 they react with PhLi in this tautomeric form to give hydroxyaminooximes **2d,e**, one of which (**2d**) has been isolated in the individual state. In the case of imidazoline **1e**, compound **9** was obtained, which could not be oxidized with MnO_2 to yield the nitroxyl radical. The structure of **9** was confirmed by the ^1H and ^{13}C NMR spectra.

Thus, we showed that the derivatives of 3-imidazoline 3-oxide existing in the cyclic form **1** add phenyllithium at the nitrone group of the heterocycle. When the acyclic form **3** prevails, the addition of phenyllithium occurs at the nitrone group of this form.

Experimental

IR spectra were recorded on a Specord M-80 spectrophotometer in KBr pellets (the concentration was 0.25 %) or in solutions (5 % in CCl_4). UV spectra were obtained on a Specord UV-VIS spectrometer in EtOH. ^1H and ^{13}C NMR spectra were run on a Bruker AC-200 spectrometer in $CDCl_3$ or DMSO-d_6 (the concentration was 5 %). The paramagnetic properties of the compounds synthesized were determined on a Minsk-12M ESR spectrometer. Compounds **1** were prepared according to the known procedures.[3,4] The characteristics of the compounds synthesized are given in Table 1, the yields correspond to purified samples.

4,4-Dimethyl-2-(2-pyridyl)-5-phenyl-4*H*-imidazole 1-oxide (10). A solution of 1.94 g (10 mmol) of hydroxyaminooxime **11** and 1.6 g (15 mmol) of pyridine-2-carbaldehyde in 30 mL of MeOH was boiled for 3 h and concentrated. Compound **10** was isolated by chromatography on a column with silica gel using $CHCl_3$ as the eluent. ^1H NMR ($CDCl_3$), δ: 1.70 (s, 6 H, CH_3); 7.4–8.8 (m, 9 H, C_6H_5, 2-pyridyl); ^{13}C NMR ($CDCl_3$), δ: 25.08 (CH_3); 73.02 (C(4)); 124.25–150.18 (m, C_6H_5, 2-pyridyl); 158.05 (C(5)); 160.61 (C(2)).

The reaction of 3-imidazoline 3-oxides (1 or 3) with phenyllithium (general procedure). 3 mmol of imidazoline **1** was added portionwise to a stirred solution of phenyllithium prepared from 1.6 mL (15 mmol) of PhBr and 0.21 g (30 mg-at.) of Li in 30 mL of abs. ether. The mixture was stirred for 30 min at 20 °C, diluted with 10 mL of water, the organic layer was separated, and the aqueous layer was extracted with ether (2×20 mL). The combined extract was dried with $MgSO_4$ and concentrated. In the case of ***N*-(2-hydroxyimino-1,1-dimethylphenethyl)-*N*-diphenylmethylhydroxylamine (2d)** the residue was washed with hexane and the precipitate of **2d** was filtered off. ^1H NMR ($CDCl_3$), δ: 1.21 (s, 6 H, CH_3); 4.67 (br.s, 1 H, OH); 5.25 (s, 1 H, $CHPh_2$); 7.3 (m, 15 H, C_6H_5); 8.47 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 23.39 (CH_3); 66.44 ($C(CH_3)_2$); 67.59 ($CH(C_6H_5)_2$); 126.21–129.17, 134.61, 143.69 (C_6H_5), 160.54 (C=N).

4,4-Dimethyl-5,5-diphenyl-2-(2-pyridyl)-2-imidazolin-1-oxyl (6). The ethereal extract prepared by the general procedure was treated with 2 g of MnO_2 for 40 min at 20 °C. The excess of the oxidizing agent was filtered off, and compound **6** was isolated by chromatography on a column with silica gel using a hexane–ethyl acetate mixture (1:2) as the eluent. The reaction of 4*H*-imidazole 1-oxide **10** with phenyllithium followed by oxidation as described above afforded compound **6** in 45 % yield.

2,4,4-Trimethyl-5,5-diphenyl-2-imidazolin-1-oxyl 3-oxide (7b) was prepared under the conditions given above and purified by chromatography on a column with silica gel using

Table 1. Characteristics of the compounds synthesized

Compound	Yield (%)	M.p.[a] /°C	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (log ε)	Molecular formula	Found / Calculated (%)		
						C	H	N
2d	90	139–141	1600 (C=N), 3590, 3200–3400 (OH)	—	$C_{23}H_{24}N_2O_2$	76.3 / 74.7	6.8 / 6.7	7.7 / 7.8
6	40	97–99	1560, 1570, 1595 (C=C, C=N)	267 (3.90) 305 (3.48)	$C_{22}H_{20}N_3O$	77.6 / 77.2	6.1 / 5.9	12.3 / 12.3
7b	50	108–110	1490, 1530 (C=N)	324 (4.08) 575 (3.28)	$C_{18}H_{19}N_2O_2$	73.4 / 73.2	6.6 / 6.4	9.5 / 9.5
8	20[b]	192–193	1490 (C=N)	267 (4.0) 327 (4.32) 340 (4.29) 555 (2.78)	$C_{34}H_{32}N_4O_4$[c]	73.1 / 72.9	5.9 / 5.7	9.9 / 10.0
9	60	140–142	1515, 1560 (C=C, C=N), 3310 (NH)	292 (4.05)	$C_{21}H_{20}N_2O_2$	75.8 / 75.9	6.2 / 6.0	8.4 / 8.4
10	60	144–146	1565, 1590, 1660 (C=C, C=N)	243 (4.10) 266 (4.08) 344 (3.99)	$C_{16}H_{15}N_3O$	72.2 / 72.4	5.4 / 5.7	15.7 / 15.9

[a] Compounds **2d**, **9**, and **10** were recrystallized from a hexane–ethyl acetate mixture; **6** and **7b** were recrystallized from heptane; compound **8** was purified by chromatography. [b] The yield is based on the amount of **1a** taken for the reaction. [c] Molecular weight (ebullioscopic): found 530, calculated 560.

an ethyl acetate—hexane mixture (1:3) as the eluent.

To prepare compound **7a**, imidazoline **1a** was added to the solution of phenyllithium, then 20 mL of abs. THF was added dropwise to the stirred reaction mixture, which was then worked up as described above. Compound **7a** was not isolated in the individual state. The IR and UV spectra of compounds **7a** and **7b** are similar.

Bis(4,4-dimethyl-5,5-diphenyl-2-imidazolin-1-oxyl-2-yl) 3,3-dioxide (8). 1 g of $K_3Fe(CN)_6$ was added portionwise to a stirred suspension of 0.5 g of crude imidazoline **7a** and 0.3 g of NaH in 10 mL of dry DMF. The mixture was stirred for 30 min at 20 °C, poured into 50 mL of water, and extracted with $CHCl_3$ (3×20 mL). The extract was washed with water (5×10 mL), dried with $MgSO_4$, and concentrated. The product was purified by chromatography on a column with silica gel using $CHCl_3$ as the eluent.

5,5-Dimethyl-2,4-diphenyl-2-(2-furyl)-3-imidazoline 3-oxide (9) was prepared in a way similar to the synthesis of compound **2d** and purified by chromatography on a column with silica gel using an ether—hexane mixture (1:1) as the eluent. ^{1}H NMR (DMSO-d_6), δ: 1.34 (s, 3 H, CH_3); 1.60 (s, 3 H, CH_3); 3.87 (s, 1 H, NH); 6.19 (m, 1 H, 3-H, furyl); 6.45 (m, 1 H, 4-H, furyl); 7.4—8.2 (m, 11 H, C_6H_5, 5-H, furyl). ^{13}C NMR (DMSO-d_6), δ: 28.25 (CH_3); 62.85 (C(5)); 91.02 (C(2)); 110.48, 112.32 (C(3), C(4), furyl); 127.25—129.60 (C_6H_5); 139.61 (C(4)); 142.13, 143.87 (C(2), C(5), furyl).

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