Reactions of metallated 1-hydroxy-2,2,4,5,5-pentamethyl-2,5-dihydro-1*H*-imidazole with functionalized nitroxyl radicals derived from 2,5-dihydro-1*H*-imidazole and 2,5-dihydro-1*H*-imidazole 3-oxide

V. A. Reznikov

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, 9 prosp. Akad. Lavrent'eva, Russian Federation. Fax: +7 (383 2) 34 4752. E-mail: mslf@nioch.nsc.ru

The reactions of the dianion generated from 1-hydroxy-2,2,4,5,5-pentamethyl-2,5-dihydro-1*H*-imidazole under the action of lithium diisopropylamide with nitroxyl radicals derived from 2,5-dihydro-1*H*-imidazole or 2,5-dihydro-1*H*-imidazole 3-oxide and containing the ester, aldehydo, cyano, or imino groups afforded biradicals, including those containing the enamino ketone and enamino imine functions. The reactions of this dianion with nitriles derived from 2,5-dihydro-1*H*-imidazole 3-oxide gave rise to an enamino nitrile, *i.e.*, electrophilic cyanation formally occurred.

Key words: nitroxyl radicals, biradicals, 2,5-dihydro-1*H*-imidazole-1-oxyl, 2,5-dihydro-1*H*-imidazole-1-oxyl 3-oxide, enamino ketones, enamino imines, electrophilic cyanation.

Previously,[1] we have demonstrated that metallated derivative **1**, which was generated by the reaction of 1-hydroxy-2,2,4,5,5-pentamethyl-2,5-dihydro-1*H*-imidazole (**2**) with LDA or phenyllithium, reacted with different electrophilic reagents. Subsequent oxidation of the reaction products afforded a wide range of functionally substituted nitroxyl radicals of the 2,5-dihydro-1*H*-imidazole and imidazolidine series, in particular, conjugated enamines, *viz.*, nitroenamines, enamino imines, enamino thiones, and enamino ketones. The latter are of considerable interest as paramagnetic ligands in coordination chemistry. These ligands were used in the synthesis of coordination compounds with transition metal ions possessing unusual magnetic properties.[1] As part of our continuing studies of the reactions of compound **1** with electrophilic reagents, we investigated its reactions with functionalized 2,5-dihydro-1*H*-imidazoles and 2,5-dihydro-1*H*-imidazole 3-oxides containing the nitroxyl radical center, which would result in the corresponding conjugated enamines. The latter could serve as paramagnetic ligands in coordination chemistry. Coordination compounds with such ligands exhibit magnetic properties due to interactions between the paramagnetic centers of different nature, *viz.*, between the nitroxyl group and the metal ion. The presence of the second nitroxyl-containing fragment in the ligand can substantially modify the properties of the synthesized complexes. In this connection, the present study was aimed at preparing biradicals containing groups which can be involved in chelate formation, *i.e.*, potential paramagnetic ligands.

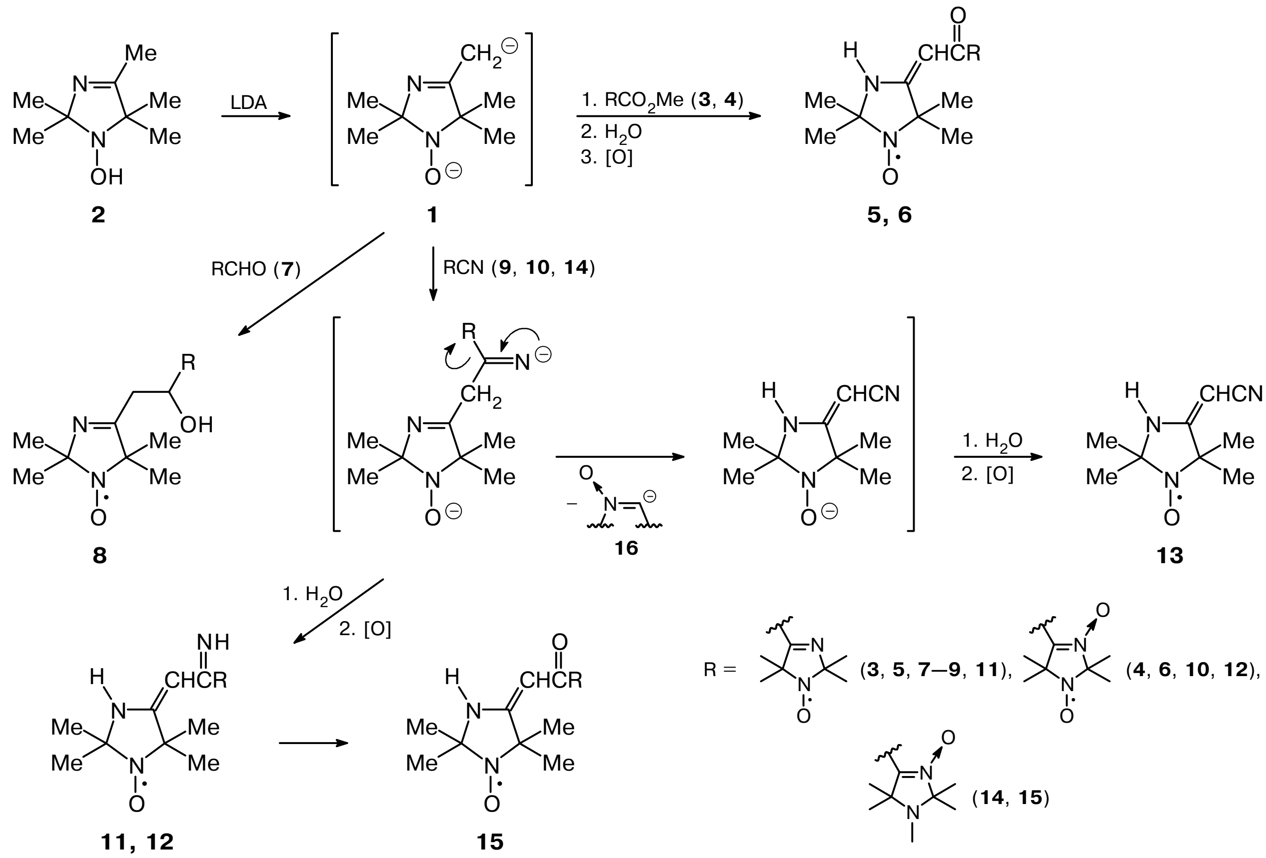
Results and Discussion

In addition to the nitroxyl group, all compounds under study contained two groups at which molecule **1** can add, *viz.*, the exocyclic functional group and the C=N bond in the heterocycle. Taking into account that the multiple bond is sterically hindered, it would be expected to remain intact in the addition reaction, and this was actually the case (*cf.* Ref. 2). Thus the reactions of compound **1** with esters **3** and **4** afforded, as expected, enamino ketones, *viz.*, biradicals **5** and **6**, respectively (Scheme 1).

The reaction with aldehyde **7** gave rise to alcohol **8**. Unexpectedly, the composition and the structures of the reaction products of compound **1** with nitriles **9** and **10** depended on the presence of the *N*-oxide group in the starting nitrile. As expected, the reaction of compound **1** with nitrile **9** afforded enamino imine **11**. However, the reaction of compound **1** with nitrile **10** produced the corresponding enamino imine **12** only in low yield, whereas enamino nitrile **13** was obtained as the major product (*cf.* Ref. 3). When the reaction time was increased to 10 h, enamino imine **12** was not isolated at all and, correspondingly, enamino nitrile **13** was obtained in higher yield. This direction of the reaction is rather unusual and one cannot say with certainty whether the imidazolidine fragment of molecule **13** originated from the metallated derivative **1** or from nitrile **10**. To answer this question, we performed the reaction of dianion **1** with 4-cyano-1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-imidazole 3-oxide **14**, and paramagnetic nitrile **13** was

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 639—642, April, 2001.

Scheme 1

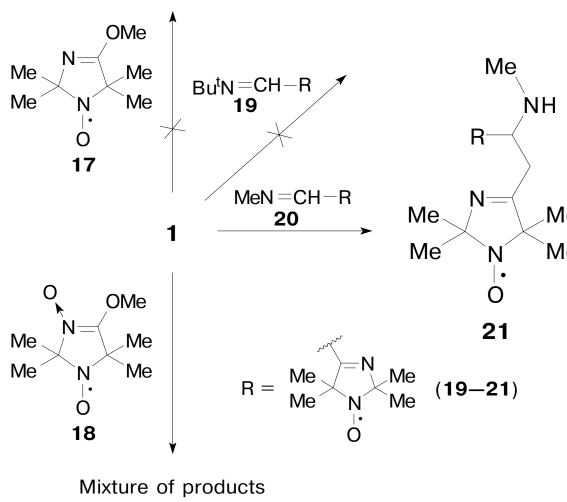


obtained as the major product, which proved that the imidazolidine fragment originated from the metallated derivative **1**. In addition to nitrile **13**, we obtained small amount of enamino ketone **15**, which is the hydrolysis product of the enamino imine formed initially. Therefore, the observed conversion **1** → **13** can be formally considered as the "electrophilic cyanation." Apparently, the reaction follows this route due to the possibility of elimination of a rather stable "dipole-stabilized" anion of the type **16** in the case of cyano derivatives of 2,5-dihydro-1*H*-imidazole 3-oxide.[4]

Under analogous conditions, methoxy imine **17** did not react with the metallated derivative **1** and was recovered from the reaction mixture in virtually quantitative yield (Scheme 2). The reaction of compound **1** with methoxy nitrone **18** afforded a complex mixture of unidentified products. The addition of molecule **1** at the C=N bond of the *N-tert*-butylimino group in compound **19** did not occur due apparently to unfavorable steric characteristics of both components. Actually, we succeeded in performing the addition of compound **1** under analogous conditions on going from *N-tert*-butylimine **19** to *N*-methylimine **20**, which resulted in secondary amine **21**.

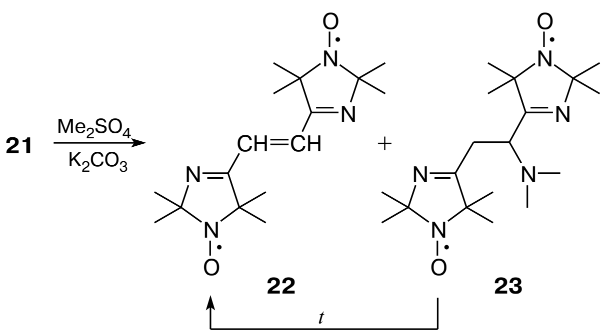
We failed to perform acid-catalyzed dehydration of alcohol **8** to obtain symmetrical biradical **22**. Apparently, amine **21** can be used as a precursor of **22** after its

Scheme 2



conversion into the trimethylammonium salt followed by the Hoffmann degradation. However, the reaction of amine **21** with 2 equivalents of dimethyl sulfate in the presence of potassium carbonate smoothly afforded dimethylamino derivative **23** and small amount of the desired biradical **22** (Scheme 3). Apparently, compound **22** was not obtained *via* the ammonium salt; instead, it is the dimethylamino derivative **23** that underwent smooth direct elimination of dimethylamine. Actually, in attempting to recrystallize amine **23** from a hexane—ethyl acetate mixture, we observed its conversion into biradical **22** in quantitative yield. Biradical **22** was also directly prepared in 80% yield by the reaction of compound **21** with dimethyl sulfate at 20 °C when the reaction time was increased to two weeks.

Scheme 3



Experimental

The IR spectra were recorded on a Bruker IFS 66 spectrometer in KBr pellets (the concentration was 0.25%, the thickness of the pellet was 1 mm). The UV spectra were measured on a Specord M-40 spectrometer for solutions in EtOH. The ESR spectra were obtained on a Bruker ESP-300 spectrometer for solutions in $CHCl_3$. The syntheses of compounds **2—4**, **7**, **9**, **10**, **14**, and **17—20** have been reported previously.[5] Diethyl ether (narcosis grade) was dried successively with $CaCl_2$ and metallic sodium. Technical grade chloroform was dried with $CaCl_2$ and distilled. Diisopropylamine (Merck) was dried with NaOH. Cromatographic purification of the compounds synthesized was carried out on KSK silica gel ground at the pilot plant of the N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry and activated by calcination at 110—120 °C for 6 h. Intermediate hydroxyamino derivatives were oxidized to radicals with manganese(IV) oxide (catalyst grade, TU-6-09-01-718-87). In all cases, the solutions were concentrated *in vacuo* with the use of a water-aspirator pump. The yields and physicochemical characteristics of the synthesized compounds are given in Table 1.

1-(2,2,5,5-Tetramethyl-2,5-dihydro-1*H*-imidazol-4-yl-1-oxyl)-2-(2,2,5,5-tetramethyl-1-oxylimidazolidin-4-ylidene)ethanone (5), 2-(2,2,5,5-tetramethyl-1-oxylimidazolidin-4-ylidene)-1-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazol-4-yl-1-oxyl 3-oxide)ethanone (6), 1,2-bis(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazol-4-yl-1-oxyl)ethanol (8), 4-[2-(2,2,5,5-tetramethyl-1-oxylimidazolidin-4-ylidene)-1-iminoethyl]-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazole-1-oxyl (11), 4-[2-(2,2,5,5-tetramethyl-1-oxylimidazolidin-4-ylidene)-1-iminoethyl]-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazole-1-oxyl 3-oxide (12), 2,2,5,5-tetramethyl-4-[2-(1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-imidazol-4-yl 3-oxide)-2-oxoethyl]imidazolidine-1-oxyl (15), and 4,4′-methylaminoethane-1,2-diylbis(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazole-1-oxyl) (21). Diisopropylamine (3.5 mL, 25 mmol) was added dropwise with stirring to a solution of phenyllithium, which was

Table 1. Physicochemical characteristics of the compounds synthesized

Compound	Yield (%)	M.p.[a] /°C	Found/Calculated (%) C	H	N	Molecular formula	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (logε)	ESR, a_N/G
5	75	248—250	59.61	8.13	17.38	$C_{16}H_{26}N_4O_3$	1627, 1607, 1553	232 (3.91)	7.3 (q)
			59.58	8.08	17.44		(N—C=C—C=O, C=N)	344 (4.17)	
6	35	238—239	56.79	7.74	16.56	$C_{16}H_{26}N_4O_4$	1602, 1585, 1554, 1515	241 (4.02)	7.1 (q)
			56.83	7.70	16.62		(N—C=C—C=O, C=N)	290 (3.60)	
								371 (4.12)	
8	50	>300	59.24	8.70	17.27	$C_{16}H_{28}N_4O_3$	1630 (C=N); 3387 (OH)	240 (3.62)	7.3 (q)
		(decomp.)	59.34	8.68	17.31				
11	90	243—244	59.79	8.47	21.79	$C_{16}H_{27}N_5O_2$	1620, 1575, 1555, 1525	225 (4.19)	7.1 (q)
			59.83	8.41	21.82		(N—C=C—C=N,	342 (4.20)	
							C=N); 3440 (NH)		
12	10	216—218	56.95	8.07	20.76	$C_{16}H_{27}N_5O_3$	1595, 1510 (N—C=C—C=N);	228 (3.93)	7.2 (q)
			56.88	8.00	20.84		3320 (NH)	287 (3.93)	
								382 (3.98)	
15	10	187—188	57.44	8.79	15.76	$C_{17}H_{29}N_4O_3 \cdot H_2O$	1627, 1576 (N—C=C—C=O);	239 (3.83)	14.6 (t)
			57.22	8.68	15.81		3290 (NH)	334 (4.05)	
21	60	127—129	60.51	9.26	20.75	$C_{17}H_{31}N_5O_2$	1635 (C=N); 3324 (NH)[b]	—	7.3 (q)
			60.53	9.23	20.81				
22	80	237—239	62.72	8.55	18.29	$C_{16}H_{26}N_4O_2$	1590 (C=C—C=N);	256 (4.32)	7.5 (q)
			62.34	9.11	18.24		3064 (=CH)		
23	50						1635 (C=N)	—	6.5

[a] The synthesized compounds were purified by recrystallization from ethyl acetate (**5**, **11**, and **12**), an ethyl acetate—chloroform mixture (**6**), a hexane—ethyl acetate mixture (**8** and **10**), or hexane (**21**).
[b] The spectrum was recorded for a solution in CCl_4.

prepared from bromobenzene (2.6 mL, 25 mmol) and lithium (0.35 g, 50 mg-at.), in diethyl ether (30 mL) at 20 °C and the mixture was stirred at this temperature under argon for 15 min. A solution of dihydroimidazole **2** (1.56 g, 10 mmol) in ether was added with stirring to the resulting solution of LDA so as to maintain slight boiling of the solvent. The reaction mixture was stirred at 20 °C for 15 min and cooled to 0 °C. A solution of the electrophile (5 mmol) in a minimum volume of ether was added in one portion to the reaction mixture. Compound **4** was added without a solvent. The mixture was stirred at 0 °C for 15 min and then at 20 °C for 1—2 h. Then water (20 mL) was added to the reaction mixture. The organic layer was separated and the aqueous solution was extracted with $CHCl_3$ (3×25 mL). In the synthesis of enamino ketone **6**, the aqueous solution was preliminarily acidified with 5% HCl to pH 5. In the synthesis of enamino ketone **5**, the combined extracts were concentrated without drying. In all other cases, the extracts were dried with $MgSO_4$ and then concentrated. Chloroform (30 mL) and MnO_2 (5 g, 57 mmol) were added to the residue. The suspension was stirred at 20 °C for 20 min and then filtered. The filtrate was concentrated. The residue was triturated with hexane (10 mL). Products **5**, **6**, **8**, and **11** were filtered off and purified by filtration of their solutions in $CHCl_3$ through a layer of silica gel (10 cm) using $CHCl_3$ as the eluent. A mixture of enamino imine **12** and nitrile **13** formed in the reaction of compound **1** with nitrile **10** was separated by column chromatography on silica gel with $CHCl_3$ as the eluent. Nitrile **13** was obtained in 55% yield. When the reaction was carried out for 10 h, nitrile **13** was obtained in 65% yield. A mixture of enamino ketone **15** and nitrile **13** was separated by column chromatography on silica gel with a 2 : 1 hexane—ethyl acetate mixture as the eluent. The yield of the nitrile was 60%. Amine **21** was isolated by column chromatography on Al_2O_3, the eluent being successively changed from hexane to $CHCl_3$ and then to a mixture of $CHCl_3$ with MeOH (30 : 1).

The reaction of metallated derivative **1** with methoxy nitrone **18** was carried out under analogous conditions.

4,4′-Dimethylaminoethane-1,2-diylbis(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazole-1-oxyl) (23) and 4,4′-vinylenebis(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazole-1-oxyl) (22). A mixture of amine **21** (0.4 g, 1.19 mmol), Me_2SO_4 (0.25 mL, 2.4 mmol), and anhydrous K_2CO_3 (0.37 g) in acetone (5 mL) was stirred at 20 °C for 72 h. The precipitate was filtered off and washed with acetone. The filtrate was concentrated. The residue was chromatographed on a column with silica gel ($CHCl_3$ as the eluent) and amine **23** was isolated in a yield of 0.25 g. The residue containing biradical **22** was successively washed with propan-2-ol, water, propan-2-ol, and ether and dried in air. The yield of **22** was 0.11 g (40%).

The reaction performed with the same amounts of the initial compounds at 20 °C for two weeks afforded only biradical **22**, which was isolated in 80% yield as mentioned above.

References

1. L. B. Volodarsky, V. A. Reznikov, and V. I. Ovcharenko, *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Boca Raton, 1994, 225 pp.
2. D. St. C. Black, V. M. Clark, R. S. Thakur, and A. Todd, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1951.
3. V. A. Reznikov, I. Yu. Bagryanskaya, and Yu. V. Gatilov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 901 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 899].
4. M. A. Voinov, I. A. Grigor′ev, and L. B. Volodarsky, *Heterocycl. Commun.*, 1998, **4**, 261.
5. L. B. Volodarsky, I. A. Grigor′ev, S. A. Dikanov, V. A. Reznikov, and G. I. Shchukin, *Imidazolinovye nitroksil′nye radikaly* [*Imidazole Nitroxyl Radicals*], Nauka, Siberian Branch, Novosibirsk, 1988, 216 pp. (in Russian).

Received April 26, 2000;
in revised form November 1, 2000