Heterocyclization Reaction of α-Imino Carbonyl Compounds − Derivatives of 2,5-Dihydro-1*H*-imidazole Nitroxides

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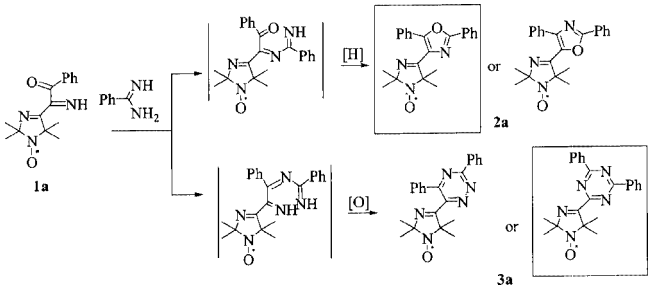
α-Imino carbonyl compounds – derivatives of 3-imidazoline nitroxides – were found to undergo heterocyclization reactions, yielding oxazole and 1,3,5-triazine derivatives. The most probable course of the reaction was suggested by the radioactive label method. The structures of the heterocycles synthesized were verified by X-ray analysis of the mixed-ligand complexes with copper hexafluoroacetylacetonate.

Stable nitroxides have been the subject of intense investigation during the last four decades. The reason for this interest was initially the singularity of this class of compounds, connected to their paramagnetism.[1] Very soon, though, chemists found out that the majority of organic reactions involving nitroxides as substrates proceed to a great extent just the same as with diamagnetic compounds.[2] In such a transformation, a nitroxyl group is simply one more functional group in a molecule, often not taking part in the transformations and very rarely (but not always[3]) even affecting them. The next phase of the development of nitroxide chemistry was, and currently is, dictated by very wide possibilities of application of nitroxides for solving different scientific problems that in fact are outside the field of synthetic organic chemistry. The main applications of nitroxides lie in the fields of biochemistry, biophysics, and molecular biology (spin labels and probes etc.).[4] Another very important field is the use of nitroxides as paramagnetic ligands for coordination chemistry. In this connection the synthesis of nitroxides of different topologies, and also differing in the presence of various functional groups in the molecule, is an active field of study. It also should be noted that information obtained from investigation of the chemical properties of functional groups in nitroxide molecules can be generalized to other classes of organic compounds and so is of general interest.

Previously we had found that treatment of imino ketone **1a** with benzamidine results in the formation of compounds **2a** and **3a**. The structures of oxazole **2a** and triazine **3a** were not determined unambiguously − the positions of the heteroatoms in the heterocycles formed were attributed arbitrarily, based only on the scheme, which is speculative in nature. The formation of compounds **2a** and **3a** was attributed to the reduction or oxidation of corresponding intermediates, formed as a result of nucleophilic attack of the amidine nitrogen atom at the carbonyl atoms of the imino or carbonyl groups in the molecule of **1a** (Scheme 1).[5]



Scheme 1

In the context of some current work the investigation of a transformation as described above was extended, and compound **3a** was in fact shown to be a 1,3,5-triazine derivative. The structure of triazine **3a** was determined by X-ray diffraction analysis of the mixed-ligand complex of **3a**

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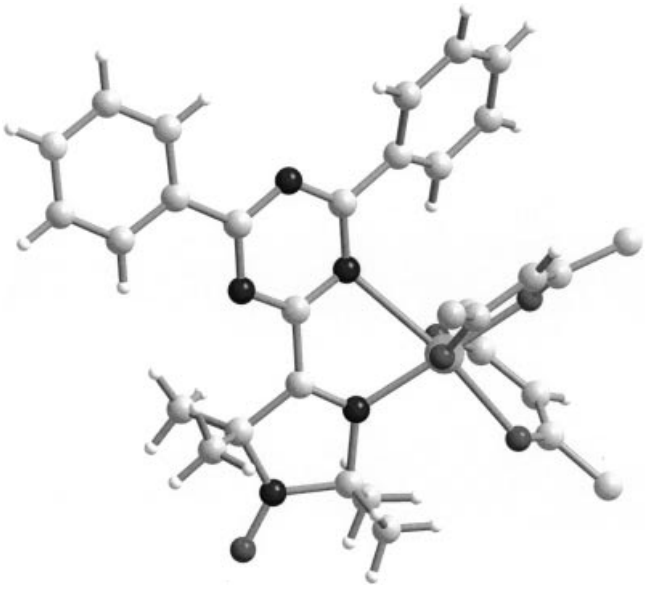
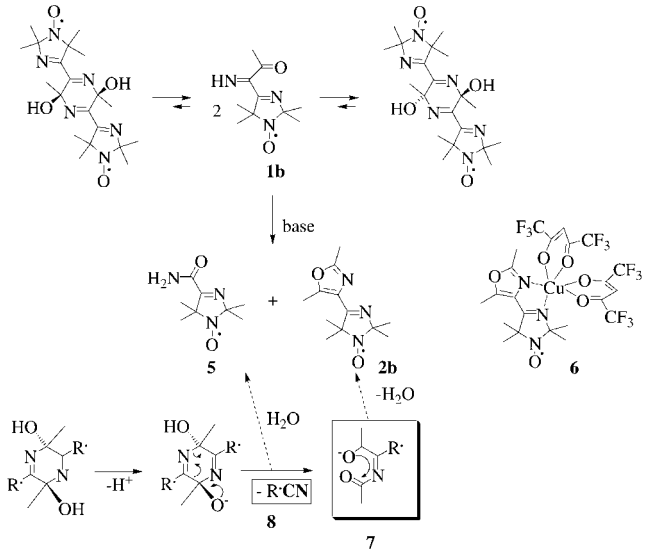


Figure 1. Crystal structure of the copper complex **4** of 4-(4,6-diphenyl-1,3,5-triazin-2-yl)-2,2,5,5-tetramethyl-2,5-dihydroimidazol-1-oxyl (**3a**) and hfac



Scheme 2

and copper hexafluoroacetylacetonate [$Cu(hfac)_2$] (**4**), the structure of which is shown in Figure 1.

It should be noted that 1,3,5-triazine formation could only be the result of a skeleton transformation of the starting molecule **1a** and, consequently, that the previously postulated reaction scheme for **1a** and benzamidine could not be entirely valid.

The methyl-substituted α-imino ketone **1b**, unlike imine **1a**, exists as a dimer in both its solution and its crystalline forms, and both diastereomeric forms are present in equilibrium in solution.[5] Thus, one could suppose that the chemical behavior of **1b** should be similar to that of **1a**. In spite of this, treatment of **1b** with benzamidine was found to proceed with formation of oxazole **2b**, which does not have a phenyl group attached to the oxazole cycle, and amide **5**. Moreover, treatment of **1b** with different nucleophiles − ethylenediamine, *o*-phenylenediamine, triethylamine, ammonium acetate − resulted in the formation of the same set of products: oxazole **2b** and amide **5** (cf. ref.[5]). Thus, the nucleophile in this transformation seems to act simply as a base (Scheme 2). The structure of oxazole **2b** was determined by single-crystal X-ray diffraction analysis of the mixed-ligand complex **6** of **2b** and $Cu(hfac)_2$, the structure being shown in Figure 2. It should be noted that the IR and UV spectra of compounds **2a** and **2b** are very similar, which could indicate that these compounds possess similar structures − imidazoline substituent in both cases being attached to the 4-position of the oxazole ring − and, hence, despite the incorrect interpretation of the reaction pathway of **1a** with benzamidine, that the structure of **2a** in ref.[5] was determined correctly.

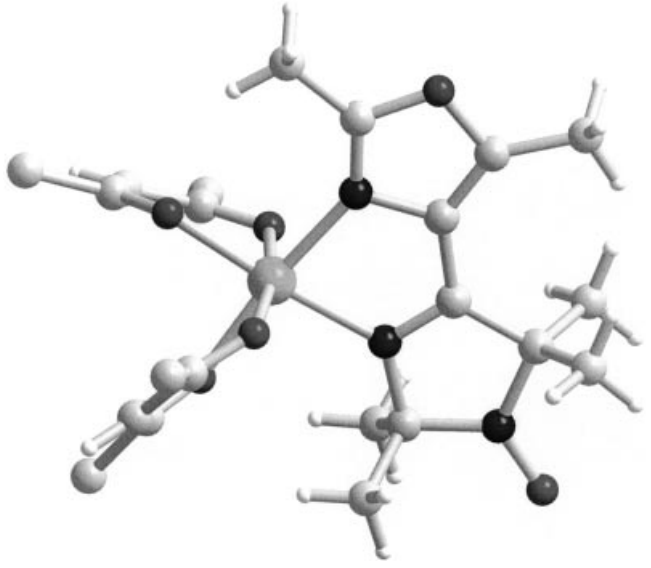
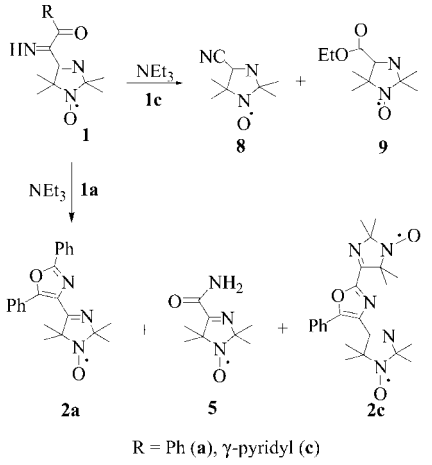


Figure 2. Crystal structure of the copper complex **6** of 4-(2,5-dimethyloxazol-4-yl)-2,5,5-trimethyl-2,5-dihydroimidazol-1-oxyl (**2b**) and hfac (fluorine atoms omitted)

The first step of the reaction is apparently a deprotonation of the hydroxy group, which results in dihydropyrazine heterocycle cleavage. Subsequent hydrolysis of intermediate nitrile **8** results in the formation of an amide **5** (cf. ref.[6]), and cyclization of intermediate **7** results in the oxazole heterocycle closure.

Imine **1c**, on being heated in the presence of triethylamine in ethanol solution, is transformed into nitrile **8** and ester **9**. Heating of imine **1a** in ethanol in the presence of triethylamine results in the formation of oxazole **2a** and amide **5**

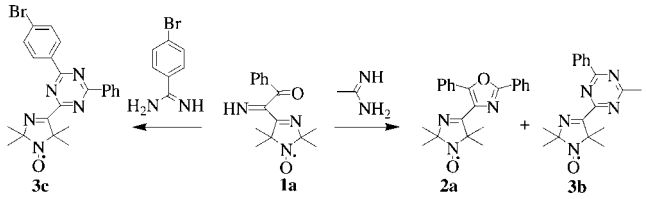


Scheme 3

along with some quantities of compound **2c** (Scheme 3). The IR and UV spectra of **2c** are similar to those of oxazoles **2a** and **2b**, and its EPR spectrum is a quintuplet with hfsc a_N = 14.6 G (in $CHCl_3$).

These data show that, although imine **1a** exists mainly in the monomeric form, some concentration of corresponding dimer **1b** is also present in solution. This concentration is obviously low (EPR spectra of **1a** correspond to a monoradical),[5] but its sufficiently high reactivity provides the possibility for its transformation into oxazole **1a** and amide **5**, similarly to the case of the dimeric imine **1b**. In this connection the question that arises is whether the formation of oxazole **2a** and triazine **3a** is a result of reaction of benzamidine with **1a** as a nucleophile, or whether benzamidine acts as a base and the products form without its direct participation.

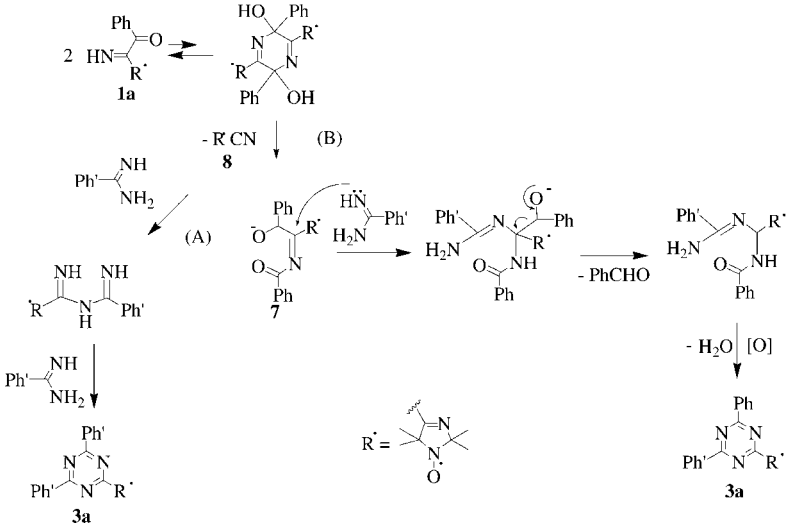
The reaction between imine **1a** and acetamidine was shown to proceed to give rise to diphenyl-substituted oxazole **2a** along with the expected monophenyl-substituted triazine **3b**. On treatment of imine **1a** with *p*-bromobenzamidine the only isolated product was the corresponding triazine **3c** (Scheme 4).



Scheme 4

It might thus be assumed that amidine participates at least in the formation of the triazine heterocycle, but it is not obvious whether, in the reaction between imine **1a** and benzamidine, both, one, or neither of the phenyl groups in the oxazole cycle originate from the benzamidine molecule, or whether some of them come from the starting material **1a**. The formation of the triazine **3** could proceed either as a result of the reaction of an intermediate nitrile **8** with 2 equiv. of amidine (path **A**), or from the intermediate **7**, postulated for the explanation of the formation of oxazole **2** (path **B**) (cf. Scheme 2). It could also not be ruled out that both routes might take place concurrently (Scheme 5).

The lack of formation of the triazine **3a** in the reaction between the nitrile **8** and benzamidine is an indirect argument against the existence of route **A**. At the same time, it should be noted that the ratio of the oxazole **2a** and the triazine **3a** formed in the reaction between imine **1a** and benzamidine depends on the ratio of reagents − an increase in the excess of benzamidine results in an increase in the comparative proportion of the triazine **3a**. At an equimolar ratio of reagents, the yields of the oxazole **2a** and the triazine **3a** are almost equal (18 and 17%, respectively). If the ratio of imine **1a** to benzamidine is 1:1.5, the yields of the oxazole **2a** and triazine **3a** are 5 and 20%, respectively. This could be interpreted as a result of two competitive processes: intermediate **7** being able to react with amidine to



Scheme 5

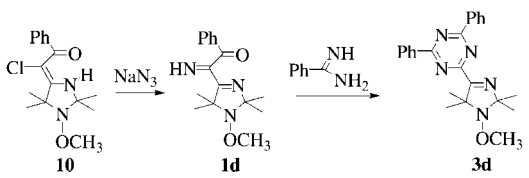
give the triazine **3a** or to undergo intramolecular cyclization with formation of the oxazole **2a**.

To clarify the question of the origins of the phenyl groups in the molecules of the oxazole **2a** and the triazine **3a**, a sample of benzamidine labeled with ^{14}C at the amidine group was synthesized and used for study of the reaction with the imine **1a**.

Direct measurement of the β-activities of the synthesized radioactive oxazole **2a*** and triazine **3a*** {Beckman β-mate scintillation counter with employment of a liquid scintillator [composition: dioxane, naphthalene, 2,5-diphenyloxazol (POP) and 1,4-bis(5-phenyloxazol-2-yl)benzene (POPOP)], concentration of **2a*** and **3a*** was ca. 10^{-2} M)} failed due to effective scintillation quenching. This phenomena could be explained by two factors: the first being the absorption of light by the nitroxyl group in the range in which scintillator photoemission takes place.[7] The second, that nitroxides are well known as quenchers of excited states,[8] also could be a reason for the diminution of measurable scintillation.

However, the addition of a nitroxide − 2,2,5,5-tetramethyl-4-phenyl-2,5-dihydroimidazol-1-oxyl ($2-5 \times 10^{-2}$ M) −, that does not contain the oxazole or triazine fragment, to the scintillator solution causes only a slight decrease in scintillator efficacy.

This implies that in the case of oxazole **2a*** and triazine **3a*** samples, some other − more efficient − mechanism of quenching is operative. The high efficiency of quenching hints that the radical may intervene at some "bottleneck" of scintillator emission, as the concentration of the radical (ca. 4 mmol/L) is much less then that of the primary (naphthalene, ca. 1.3 M) and secondary (POP, ca. 30 mmol/L) scintillators. This "bottleneck" may be the transmission of light from POP to wavelength shifter POPOP, the concentrations of the latter being noticeably smaller than the concentrations of **2a*** and **3a*** in the measured solutions (ca. 0.8 mmol/L). The compounds **2a*** and **3a*** could interfere with the scintillation if their heterocyclic substituents were to possess photoluminescent properties similar to those of POPOP. This looks quite reasonable, at least in the case of **2a**, which contains a diphenyloxazole function − exactly the same as in POPOP. We undertook a special study on this point and tried to prepare diamagnetic analogues of **2a** and **3a** by treatment of the methoxy-substituted diamagnetic imine **1d** with benzamidine (Scheme 6).



Scheme 6

Unfortunately, the only product isolated was the corresponding 1-methoxy-substituted triazine **3d**.

Measurement of the fluorescence spectra of triazine **3d** shows emission in a wide range of excitatory UV ir-

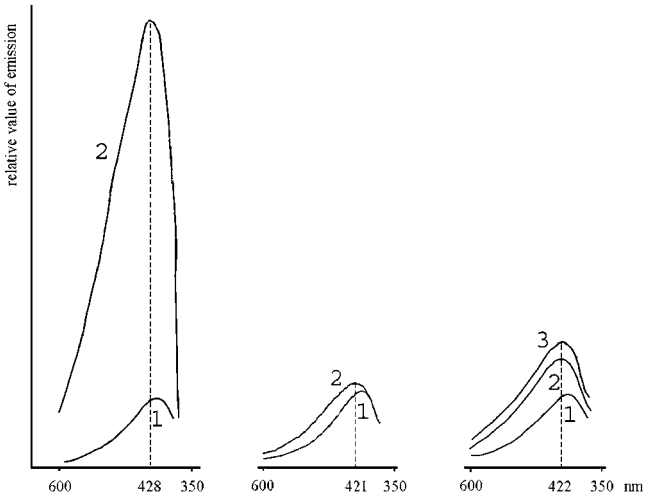


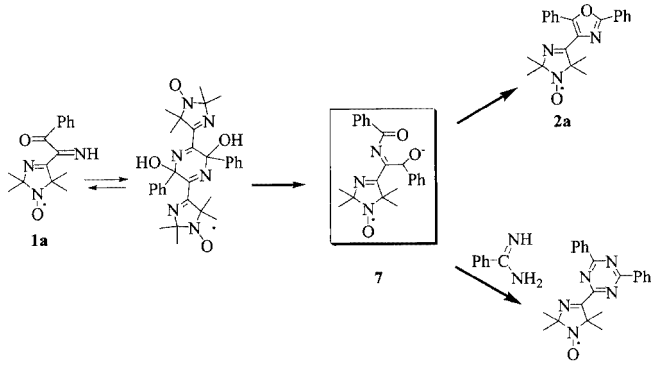
Figure 3. Fluorescence spectra (methanol, 10^{-4} M): 1 − background; left: 2 − methoxy-substituted triazine **3d**; center: 2 − triazine **3a**; right: 2 − oxazole **2a**, 3 − oxazole **2a** after addition of hydrazine hydrate (3 equiv.)

radiation, with a maximum peak of emission at λ_{em} = 428 nm, excitation being at λ_{ex} = 380 nm. In contrast to this, neither the paramagnetic triazine **3a** nor the oxazole **2a** display fluorescence ability. It should be noted that the fluorescence value of a sample of oxazole **2a** changes insignificantly on addition of excess hydrazine hydrate (Figure 3), indicating that even trace amounts of the radical provide effective quenching. Thus, it is reasonable to suppose that **2a** and **3a** suppress the scintillation of the solutions through effective intramolecular quenching of scintillation by the nitroxyl group.

In this connection, samples of β-active benzamidine hydrochloride monohydrate, oxazole **2a***, and triazine **3a*** were converted into sodium carbonate by combustion and their activities were measured by use of the scintillation counter. The activity of the sample obtained from 2.104 mg (5.65 μmol) triazine **3a** was 10.7 ± 1.2 counts/min, from 2.116 mg (5.87 μmol) oxazole **2a** 3.6 ± 1.8 counts/min, and from benzamidine (2.178 mg, 12.5 μmol) 30.0 ± 1.4 counts/min. The activities of the oxazole **2a*** and triazine **3a*** samples in the case of involvement of one phenyl group from benzamidine would be expected to be 14.3 ± 1.8 and 13.7 ± 1.8 counts/min, respectively. Thus, oxazole **2a** arises mainly without direct participation of benzamidine according to the mechanism shown in Scheme 2, although the pathway shown in Scheme 1 also takes place to some extent. As to triazine **3a** formation, the most probable seems to be pathway **B**, as shown in Scheme 5. In order to exclude the possibility of exchange of phenyl substituents in oxazole **2a** and triazine **3a** molecules as the result of subsequent reaction of these heterocycles with benzamidine, **2a** and **3a** were treated with *p*-methoxybenzamidine under the conditions of their formation. Analysis of the products obtained by high-resolution mass spectrometry shows no exchange in both cases.

Thus, the reaction between imine **1a** and benzamidine has been shown to proceed mainly through the formation

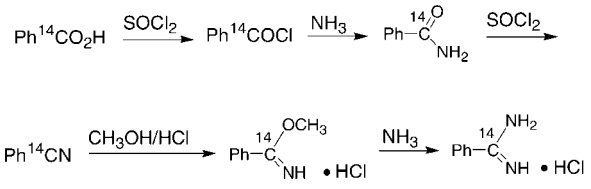
of intermediate **7**, which then either undergoes cyclization, giving rise to oxazole **2a**, or reacts with amidine to give triazine **3a** (Scheme 7). Other routes of formation of products **2**, **3** are inconsequential.



Scheme 7

Experimental Section

General: IR spectra were recorded with a Bruker IFS 66 spectrometer as KBr pellets (concentration 0.25%, thickness of a pellet 1 mm). UV spectra were measured with a Specord M-40 spectrophotometer in EtOH. ^{1}H NMR spectra were run with a Bruker WP 200 SY spectrometer with 5% solutions in $CDCl_3$ and HMDS as the internal standard. High-resolution mass spectra were recorded with a Finnigan MAT 8200 mass spectrometer with direct sample injection with resolution 10000. Melting points were measured with a "Boetius" plate and are uncorrected. DMSO was dried with NaOH and distilled in vacuo from BaO. Measurement of the β-activity was carried out with a Beckman β-mate II scintillation counter in a dioxane solutions containing naphthalene (100 g/L), 2,5-diphenyloxazole (7 g/L), and 1,4-bis(4-methyl-5-phenyloxazol-2-yl)benzene (0.3 g/L). Dioxane for measurements was dried with NaOH and distilled from sodium wire before use. Fluorescence spectra were measured with a Shimadzu RF-520 spectrophotometer in ethanol. The synthesis of imines **1a**, **1b**, **1c**, and **1e** was published in ref.[5] Benzamidine enriched with ^{14}C at the amidine group carbon atom was synthesized from $Ph^{14}CO_2H$ benzoic acid according to the standard procedure shown in Scheme 8). Benzoyl chloride was synthesized by use of an aqueous solution containing radioactive benzoic acid. A mixture of aqueous radioactive benzoic acid (5 mL), benzoic acid (10 g, 82 mmol), and benzene (100 mL) was heated at reflux in a Dean−Stark apparatus for 12 h. $SOCl_2$ (12 mL, 164 mmol) was added to the resulting solution after cooling, and the mixture was heated at reflux for 8 h. The benzene was distilled off, and the residue was distilled in vacuo to give benzoyl chloride (9.5 g, 80%), b. p. 105−107 °C (25 Torr). The synthesis of benzamidine hydrochloride monohydrate was carried out in a standard manner.



Scheme 8

Reaction between 1a and Benzamidine: Imine **1a** (0.5 g, 1.8 mmol) was added to a solution of benzamidine hydrochloride monohydrate (0.48 g, 2.8 mmol) in methanol (15 mL). The system was alkalized to pH = 11 with sodium methoxide, and the resulting solution was kept at 20 °C for 24 h. The solvent was removed in vacuo, and the residue was dissolved in water (10 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried with $MgSO_4$, the solution was concentrated in vacuo, and a mixture of products **2a** and **3a** was separated on alumina, with a hexane/ethyl acetate mixture (5:1) as eluent (cf. ref.[5]).

4-(2,5-Diphenyloxazol-4-yl)-2,2,5,5-tetramethyl-2,5-dihydroimidazol-1-oxyl (2a): The yield was 18%, m.p. 146−148 °C (from hexane). IR (KBr): $\tilde{\nu}$ = 1615, 1600, 1580 (C=N, C=C) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 233 (4.11), 286 nm (4.15). MS: calcd. for $C_{22}H_{22}N_3O_2$ *m*/*z* = 360.17119, found 360.17045.

4-(4,6-Diphenyl-1,3,5-triazin-2-yl)-2,2,5,5-tetramethyl-2,5-dihydroimidazol-1-oxyl (3a): The yield was 17%, m.p. 188−190 °C (from hexane/ethyl acetate). IR (KBr): $\tilde{\nu}$ = 1621, 1661 (C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 273 nm (4.48). $C_{22}H_{22}N_5O$ (372.2): calcd. C 70.9, H 5.9, N 18.8; found C 70.5, H 5.9, N 18.7.

Treatment of imine **1a** with radioactive benzamidine was carried out under identical conditions and with the same quantities of reagents.

2-(1-Methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*−imidazol-4-yl)-4,6-diphenyl-1,3,5-triazine (3d): Similarly, treatment of imine **1d** (1 g, 3.5 mmol) with benzamidine hydrochloride monohydrate (1 g, 5.7 mmol) resulted in the formation of **3d** in 35% yield, m.p. 160−161 °C (from hexane). IR (KBr): $\tilde{\nu}$ = 2810 (OCH_3), 1518 (C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 274 nm (4.30). $C_{23}H_{25}N_5O$ (387.2): calcd. C 71.3, H 6.5, N 18.1; found C 71.0, H 6.4, N 18.0.

X-ray Crystallography of Compounds 4 and 6: Atomic coordinates, thermal parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Center. CCDC-207326 and -207327 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. It may be noted that according to CSD[9] the Cu−O distance to axial oxygen O(5) is shorter than 2.232 Å,[10] the minimum value in analogous $Cu(HFA)_2$ complexes with similar five-membered metallacycles.

2-Imino-2-(1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-imidazol-4-yl)-1-phenyl-ethanone (1d): Enaminone **10** (1.3 g, 4.2 mmol) was added to a solution of NaN_3 (0.55 g, 8.4 mmol) in DMSO (10 mL). The reaction mixture was stirred at 20 °C for 2.5 h, then cooled to 0 °C and poured into cold brine (40 mL). The resulting mixture was extracted with $CHCl_3$ (3 × 20 mL), and the combined extracts were washed with brine and water and dried with $MgSO_4$. The solution was concentrated to give imine **1d** (1.26 g, almost 100%), m.p. 73−74 °C (from hexane). IR (KBr): $\tilde{\nu}$ = 3206 (NH), 2811 (O−CH_3), 1669 (C=O) 1608, 1597, 1580 (C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 253 nm (4.06). $C_{16}H_{21}N_3O_2$ (287.2): calcd. C 66.9, H 7.4, N 14.6; found C 66.8, H 7.5, N 14.7.

2-Chloro-2-(1-methoxy-2,2,5,5-tetramethylimidazolidin-4-ylidene)-1-phenylethanone (10): NCS (0.64 g, 4.7 mmol) was added to a solution of 2-(1-methoxy-2,2,5,5-tetramethylimidazolidin-4-ylidene)-1-phenylethanone[11] (1.3 g, 4.7 mmol) in CCl_4 (20 mL), and the re-

sulting mixture was stirred at 20 °C for 30 min. Precipitated succinimide was filtered off, the filtrate was concentrated to dryness in vacuo, and the residue was recrystallized from hexane to give **10** (1.45 g, almost 100%). M.p. 127−129 °C (from hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 6 H), 1.62 [br. s, 6 H, 2,5-$(CH_3)_2$], 3.70 (s, 3 H, OCH_3), 7.37 (m, 3 H), 7.57 (m, 2 H, C_6H_5) ppm. IR (KBr): $\tilde{\nu}$ = 3210 (NH), 1594, 1538 (O=C−C=C−N, C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 243 (3.58), 343 nm (4.69). $C_{16}H_{21}ClN_2O_2$ (308.8): calcd. C 62.24, H 6.81, N 9.08; found C 62.53, H 6.85, N 9.07.

Treatment of Imine 1a with Triethylamine: A solution of imine **1a** (0.2 g, 0.74 mmol), triethylamine (0.1 mL, 0.72 mmol), and *p*-toluenesulfonic acid (5 mg) in ethanol (20 mL) was heated at reflux for 12 h and then concentrated to dryness. Reaction products were isolated by preparative thin layer chromatography on silica gel with $CHCl_3$/methanol (30:1) as eluent. The yield of oxazole **2a** was 0.06 g (45%), of oxazole **2c** 0.01 g (6%), and of amide **5** 0.006 g (8%).

Compound 2c: M.p. 223−225 °C (from hexane/ethyl acetate), IR (KB): $\tilde{\nu}$ = 1610, 1578 (C=C−C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 305 nm (4.05). $C_{23}H_{29}N_5O_3$ (423.2): calcd. C 65.2, H 6.9, N 16.5; found C 65.2, H6.7, N16.3.

On heating of a solution of imine **1c** (0.2 g, 0.73 mmol), triethylamine (0.1 mL, 0.7 mmol), and *p*-toluenesulfonic acid (5 mg) in ethanol (20 mL) for 1 h, a mixture of nitrile **8** and ester **9** was obtained. It was separated by preparative thin-layer chromatography on silica gel with $CHCl_3$/methanol (30:1) as eluent. The yield of **8** was 0.013 g (10%) and of **9** 0.015 g (10%) The structures of **8** and **9** were confirmed by comparison with authentic samples.[7]

Treatment of Imine 1a with Acetamidine. 2,2,5,5-Tetramethyl-4-(4-methyl-6-phenyl-1,3,5-triazin-2-yl)-2,5-dihydroimidazol-1-oxyl (3b): Imine **1a** (0.5 g, 1.8 mmol) was added to a solution of acetamidine hydrochloride in ethanol (10 mL). This was alkalized to pH = 11 with sodium methoxide and the resulting mixture was kept at 20 °C for 24 h and then heated at 70 °C for 5 h. The solution was concentrated, water (5 mL) was added to the residue, and the resulting mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried with $MgSO_4$, the solution was concentrated, and the reaction products were isolated by chromatography on silica gel with $CHCl_3$/methanol (30:1) as eluent, with oxazole **2a** (0.17 g 50%) and **3b** (0.085 g, 15%) being eluted sequentially. **3b:** M.p. 125−128 °C (aqueous ethanol). IR (KBr): $\tilde{\nu}$ = 1600, 1586, 1536, 1518 (C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 237 (3.89), 263 nm (3.96). $C_{17}H_{20}N_5O$ (310.2): calcd. C 63.9, H 6.5, N 21.9; found C 64.1, H 6.3, N 22.0.

Treatment of Imine 1b with Triethylamine. 4-(2,5-Dimethyloxazol-4-yl)-2,5,5-trimethyl-2,5-dihydroimidazol-1-oxyl (2b): A solution of imine **1b** (0.5 g, 2.4 mmol), triethylamine (0.3 mL, 2.4 mmol), and *p*-toluenesulfonic acid (10 mg) in ethanol (20 mL) was heated at reflux for 2 h and then concentrated. A mixture of oxazole **2b** and amide **5** was separated by preparative thin-layer chromatography on silica gel with $CHCl_3$/methanol (30:1) as eluent to give **2b** (0.25 g, 90%) and amide **5** (0.13 g, 65%). **2b:** M.p. 136−139 °C (from hexane). IR (KBr): $\tilde{\nu}$ = 1614 (C=C−C=N) cm^{-1}. UV (ethanol=: λ_{max} (lg ε) = 252 (4.14), 372 nm (4.00). $C_{12}H_{18}N_3O_2$ (236.1): calcd. C 61.0, H 7.6, N 17.8; found C 60.6, H 7.9, N 17.8. MS: calcd. for $C_{12}H_{18}N_3O_2$ *m/z* = 236.13989, found 236.13942.

4-[4-(4-Bromophenyl)-6-phenyl-1,3,5-triazin-2-yl]-2,2,5,5-tetramethyl-2,5-dihydro-imidazol-1-oxyl (3c): Imine **1a** (0.5 g, 1.8 mmol) was added to a solution of 4-bromobenzamidine hydrochloride (0.42 g, 1.8 mmol) in methanol (10 mL). This was alkalized to pH = 11 with sodium methoxide, and the reaction mixture was kept at 20 °C for 24 h, and then concentrated. $CHCl_3$ (20 mL) was added to the residue, and the chloroform solution was washed with 0.5% HCl solution and dried with $MgSO_4$. The solution was concentrated and triazine **3c** was purified by chromatography on silica gel with $CHCl_3$ as eluent. The yield was 0.16 g (20%), m.p. 187−192 °C (from ethanol). IR (KBr): $\tilde{\nu}$ = 1590, 1578, 1515 (C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε) = 284 nm (4.24). $C_{22}H_{21}BrN_5O$ (450.1): calcd. C 58.5, H 4.7, N 15.5; found C 58.1, H 4.5, N 15.1.

[1] [1a] A. R. Forrester, J. M. Hay, R. H. Thomson, *Organic Chemistry of Stable Free Radicals*, Academic Press, New York, **1968**. [1b] E. G. Rozantsev, *Free Nitroxyl Radicals*, Plenum Press, New York, **1970**. [1c] A. L. Buchachenko, *Stable Radicals. Electron Structure, Reactivity and Applications*, Khimia, Moscow, **1973** (in Russian).

[2] M. B. Neiman, E. G. Rozantsev, Yu. G. Mamedova, *Nature* **1962**, *196*, 472.

[3] I. A. Grigor'ev, G. I. Shchukin, L. B. Volodarsky, *Studies on the effect of the radical center on the chemical reactivity, in Imidazoline Nitroxides*, vol. 1 ("Synthesis and properties") (Ed.: L. B. Volodarsky), CRC Press, Boca Raton, FL, **1989**, chapter 5.

[4] [4a] J. F. W. Keana, Nitroxide spin labels in *Spin Labeling in Pharmacology* (Ed.: J. L. Holtzmann), Academic Press, Orlando, FL, **1984**. [4b] L. J. Berliner, J. Reuben (Eds.), *Spin labeling: Theory and Applications*, vol. 1, 2, 8 and 14, Plenum Press, New York, **1976, 1979, 1989** and **1998**; L. B. Volodarsky (Ed.), *Imidazoline Nitroxides*, V, II ("Applications"), CRC Press, Boca Raton, FL, **1989.**

[5] V. A. Reznikov, G. I. Roshchupkina, T. V. Rybalova, Yu. V. Gatilov, *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 874.

[6] L. B. Volodarskii, G. A. Kutikova, V. S. Kobrin, R. Z. Sagdeev, Yu. N. Molin. *Izv. Sib. Otd. Akad. Nauk S. S. S. R., Ser. Khim. Nauk*. **1971**, 101; *Chem. Abstr.* **1972**, *76*, 153673r.

[7] L. B. Volodarsky, V. A. Reznikov, I. A. Grigor'ev, *Chemical Properties of Heterocyclic Nitroxides, in Imidazoline Nitroxides*, vol. 1 (Ed.: L. B. Volodarsky), CRC Press, Boca Raton, **1988**.

[8] G. I. Likhtenshtein, in *Biophysical Labeling Methods in Molecular Biology, Encyclopedia of Molecular Biology*, vol. 6 (Ed.: R. A. Meyers), **1995**.

[9] F. H. Allen, O. Kennard, *Chemical Design Automation News* **1993**, *8*, 31.

[10] H. Morikawa, F. Imamura, Y. Tsurukami, T. Itoh, H. Kumada, S. Karasawa, N. Koga, H. Iwamura, *J. Mater. Chem.* **2001**, *11*, 493.

[11] V. A. Reznikov, L. B. Volodarsky, *Khim. Geterosikl. Soedin.* **1990**, 921; *Chem. Heterocycl. Compd.* **1973** (Engl. Transl.).

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