Reaction of α-Hydroxyamino Ketones with Dicarbonyl Compounds – Synthesis of Imidazoline Nitroxides with a Functional Group in a Side Chain

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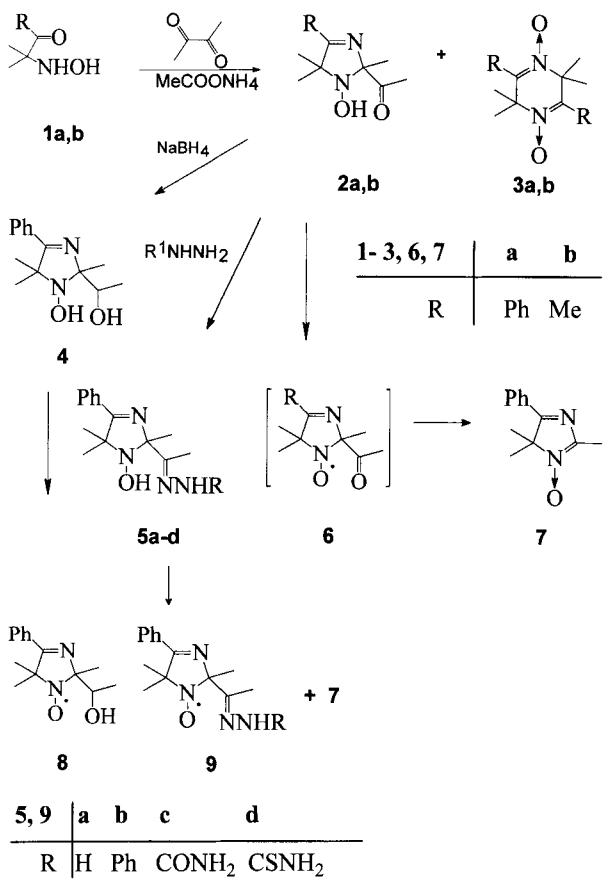
The reaction of α-hydroxyamino ketones **1** with diacetyl, acetyl acetone or acetoacetic ester in the presence of ammonium acetate results in the formation of 3-imidazoline derivatives **2**, which are precursors for the synthesis of stable nitroxides **8**, **9**, **14**, **16**, **17**, **23**–**24** with various functional groups in the side chain at the 2-position of the heterocycle.

Nitroxides of 3-imidazolines are traditionally synthesized by condensation of α-hydroxyamino ketones **1** with ketones and ammonia or ammonium acetate, followed by oxidation of the resulting 1-hydroxy-3-imidazolines. Methylalkyl, cycloalkyl, and methylaryl ketones, as well as some functionally substituted ketones, such as keto esters in which the keto group is not in a β-position with respect to the ester group, can participate in this reaction[1]. Derivatives of 3-imidazoline 3-oxide, pyrazine dioxide, and hydroxyimidazole have been shown to result from the reaction of α-hydroxyamino oximes with dicarbonyl compounds, depending on the structure of initial reactants[2]. This work is aimed at the study of the reaction of α-hydroxyamino ketone **1** with dicarbonyl compounds such as diacetyl, acetylacetone, and acetoacetic ester, as well as of the possible transformation of the resulting condensation products into stable nitroxides, with functional goups in a side chain.



Only one carbonyl groups of diacetyl participates in its reaction with α-hydroxyamino ketones **1a**, **1b** in the presence of ammonium acetate, thereby giving 2-acetyl-substituted 1-hydroxy-3-imidazolines **2a**, **2b** in yields of 38 and 22%, respectively. It is noteworthy that in this reaction also two molecules of the starting α-hydroxyamino ketone condense with each other to give considerable amounts of the dihydropyrazines **3a**, **3b** (yields of about 50%). Such behaviour was previously observed in the reaction of **1** with less reactive ketones[3].

Oxidation of 2-acetylimidazolines **2** with MnO_2 does not lead to the desired stable nitroxides **6**, but results in the formation of 4*H*-imidazole **7**. A similar observation was made in the case of 2-acyl-substituted 3-imidazoline 3-oxide derivatives and was attributed to the ease with which acyl radicals can be released[4–6]. In contrast, oxidation of 1-hydroxy-2-acetyl-3-imidazoline 3-oxide oxime, semicarbazone or thiosemicarbazone gives the corresponding stable nitroxides[4,6]. In this connection some derivatives of ketone **2a** such as hydrazone **5a**, phenylhydrazone **5b**, semicarbazone **5c**, and thiosemicarbazone **5d** were prepared and subjected to oxidation. The reaction of hydrazone **5a** with MnO_2 did not provide the corresponding stable nitroxide, as might be expected, and the oxidation of phenylhydrazone **5b** yielded only 4*H*-imidazole **7**. However, oxidation of semicarbazone **5c** and thiosemicarbazone **5d** under these conditions gave the stable nitroxides **9c**, **9d** in high yields, although imidazole **7** accumulated in the mixture with increasing reaction time. It should be noted that partial de-

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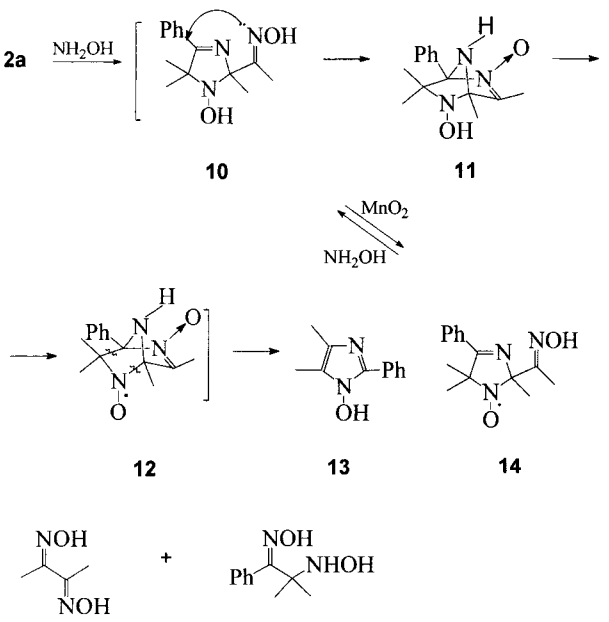
composition of compounds **9c**, **9d** occurs even in the absence of MnO_2, for instance, on attempted recrystallization, imidazole **7** was obtained as one of the decomposition products.

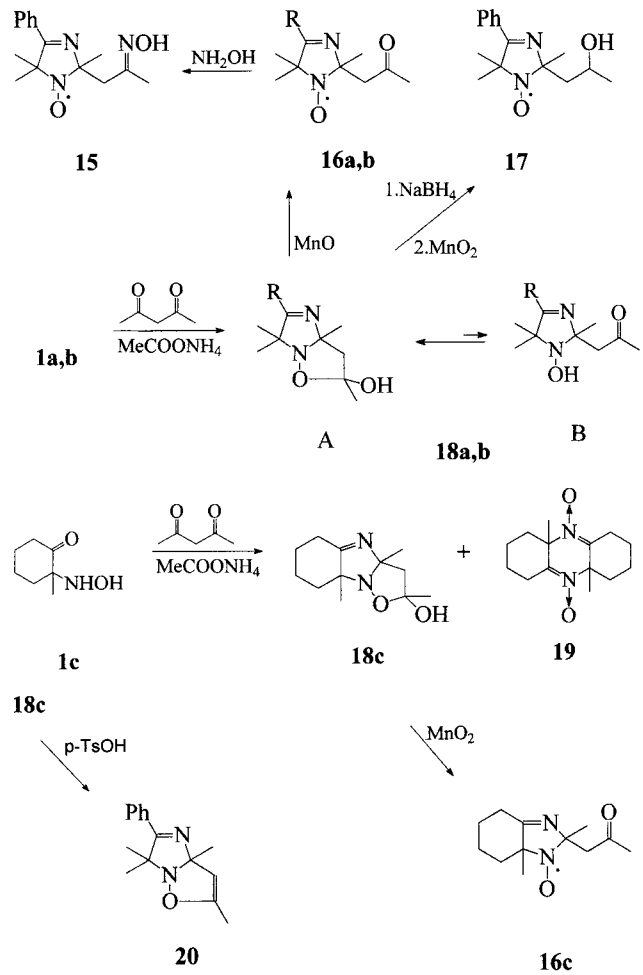
Reduction of ketone **2a** with $NaBH_4$ resulted in a mixture of diastereomeric alcohols **4** which could easily be oxidized with MnO_2 to the stable nitroxides **8**. Prolonged oxidation of **4** afforded imidazole **7** as the sole reaction product within 12 hours.

Unexpectedly, reaction of **2a** with hydroxylamine did not result in the formation of oxime **10**, but 1-hydroxyimidazole **13** was produced, as identified by comparison with an authentic sample[7]. The formation of **13** may proceed via an intramolecular attack of the nitrogen of the oxime group at C-4 to give the bicyclic derivative **11**, followed by oxidation under the reaction conditions to the nitroxide **12**, and subsequent cleavage of the nitroxyl-containing ring (cf. ref.[6]). The products of hydrolytic cleavage of the imidazoline heterocycle, dimethylglyoxime and 2-hydroxyamino-3-hydroxyimino-2-methyl-3-phenylpropane were found in the reaction mixture along with imidazole **13**.



The reaction of **2a** with hydroxylamine acetate also led to imidazole **13** as the main product, together with small amounts of oxime **10** which was isolated and identified as the nitroxyl radical **14**[8]. The generation of imidazole **13** from oxime **10** was verified by reaction of radical **14** with hydroxylamine hydrochloride in the presence of sodium methoxide. According to TLC analysis, oxime **10** seems to be the initially generated product. As the reaction proceeds, compound **10** disappears and imidazole **13** emerges as the sole product.

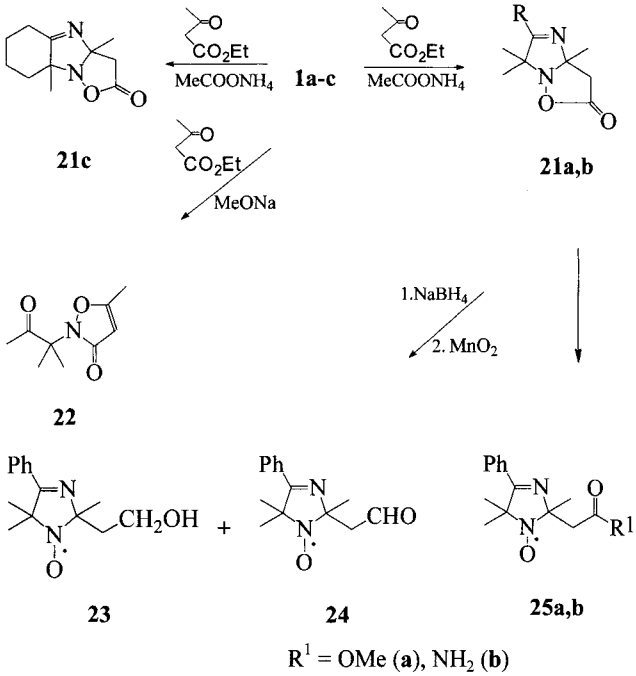
The reaction of α-hydroxyamino ketones **1a**, **1b** with acetylacetone in the presence of ammonium acetate furnished the 2-acetonyl-substituted derivatives **18a**, **18b**, which were found to exist in hemiacetal form **A** both in solution and in the solid state, according to their spectra (cf. ref.[9]). α-Hydroxyamino ketones **1** did not react with less reactive β-diketones such as benzoylacetone and dibenzoylmethane under the above conditions. This is clearly attributable to a more rapid competing reaction leading to the corresponding pyrazine **3**. Although no keto form **B** was found in the solution of **18a**, **18b**, these compounds were readily oxidized to yield stable nitroxides **16a**, **16b**. Nevertheless, the reaction times required for their complete oxidation were longer than those needed for the other 1-hydroxy-3-imidazoline derivatives. Reaction of α-hydroxyamino ketone **1c** with acetylacetone under similar conditions resulted in the formation of hemiacetal **18c**, the oxidation of which allowed the formation of the stable nitroxide **16c**. In this case the condensation reaction was also accompanied by the formation of considerable amounts of pyrazine **19**. It should be noted that the IR spectra of ketones **16a**, **16b** exhibit two carbonyl bands, which are associated with the hindered rotation about the single C–C bond, as a consequence of spatial hindrance. The IR spectrum of ketone **16c**, which is a mixture of two diastereomers, is more complex.



Hemiacetal **18a** was easily reduced by the action of $NaBH_4$, and subsequent oxidation with MnO_2 led to a mixture of diastereomeric alcohols **17**. Ketone **16a** reacted with hydroxylamine to give oxime **15** with retention at the rad-

ical center. Hemiacetal **18a** was easily dehydrated in the presence of TsOH to yield compound **20**, which can be considered as a cycloadduct of imidazole **7** with methyl acetylene. Although such derivatives tend to be unstable and readily undergo rearrangements[10], compound **20** turned out to be stable.

The reaction of α-hydroxyamino ketones **1a–1c** with acetoacetic acid ester in the presence of ammonium acetate gave lactones **21a–21c**. In this case, intramolecular *O*-acylation of heterocyclic hydroxyamino group occurs, along with condensation, proceeding with the participation of acetoacetic ester keto group, even though 1-hydroxy-imidazolines are not generally acylated with esters.



It is interesting to note that the reaction of α-hydroxyamino ketone **1b** with acetoacetic ester in the presence of CH_3ONa proceeded only with the participation of hydroxyamino group to yield isoxazoline **22**.

Lactones **21**, as expected, were not oxidized to give stable nitroxides. However, alkaline hydrolysis of compound **21a** followed by oxidation with MnO_2 and alkylation with diazomethane furnished the stable nitroxide **25a**. The reaction of **21a** with aqueous ammonia also led to lactone ring-opening, and was accompanied by oxidation to give amide **25b**. Lactones are known to be reduced with $NaBH_4$ to give either diols or aldehydoalcohols[11]. Accordingly, the reaction of lactone **21a** with $NaBH_4$ and subsequent oxidation with MnO_2 resulted in the formation of alcohol **23** and aldehyde **24**.

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Experimental Section

Melting points (uncorrected): Kofler plate. – IR Spectra: Specord M-80. – UV Spectra: Specord UV-vis. – ^{1}H- and ^{13}C-NMR spectra: Bruker AC-200 at 300 K (with solvent peaks used as internal standards). EPR Spectra: Bruker ESP 300. – Column chromatography: silica gel "KSK" made in Russia, 100–200 mesh, activated on heating at 120°C for 5 hours. In all cases solutions were evaporated under reduced pressure, and organic extracts were dried with anhydrous $MgSO_4$.

2-Acetyl-1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (**2a**): A solution of 2.0 g (11.1 mmol) of α-hydroxyamino ketone **1a**, 1.75 ml (19.8 mmol) of diacetyl, and 2.0 g (26 mmol) of ammonium acetate in 10 ml of methanol was kept at room temp. for 48 h and then evaporated. The residue was treated with 10 ml of saturated brine and 10 ml of hexane and the precipitated imidazoline **2a** was filtered off, washed with hexane and ice-water, and dried in air. The yield of **2a** was 1.0 g (38%); m.p. 137–139°C (heptane). – IR (KBr): $\tilde{\nu}$ = 1720 cm^{-1} (C=O), 1610, 1575 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 243 nm (4.06). – ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.44 (s, 3H, 2-CH_3), 1.54 (s, 3H, 5-CH_3), 1.56 (s, 3H, 5-CH_3), 2.21 (s, 3H, CH_3CO), 5.95 (br, 1H, OH), 7.43 (m, 3H), 7.80 (m, 2H, C_6H_5). – $C_{14}H_{18}N_2O_2$ (246.3): calcd. C 68.4, H 7.3, N 11.4; found C 68.2, H 7.4, N 11.4.

2-Acetyl-1-hydroxy-2,4,5,5-tetramethyl-3-imidazoline (**2b**): A solution of 2.0 g (17.0 mmol) of α-hydroxyamino ketone **1b**, 2 ml (22.8 mmol) of diacetyl, and 3.0 g (52 mmol) of ammonium acetate in 10 ml of methanol was kept at room temp. for 5 h and then evaporated. The residue was dissolved in 20 ml of saturated brine, made alkaline with Na_2CO_3 (to pH 8), and extracted with diethyl ether (5 × 15 ml). The pooled extracts were dried and evaporated. The residue was treated with a mixture of hexane/ethyl acetate 5:1, and the precipitate was filtered off and washed with hexane to yield 0.7 g (22%) **2b**; m.p. 159–160°C (ethyl acetate/hexane). – IR (KBr): $\tilde{\nu}$ = 1715 cm^{-1} (C=O), 1635 (C=N). – ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.22 (s, 3H, 5-CH_3), 1.24 (s, 3H, 5-CH_3), 1.40 (s, 3H, 2-CH_3), 1.99 (s, 3H, 4-CH_3), 2.10 (s, 3H, CH_3CO), 6.10 (s, 1H, OH). – $C_9H_{16}N_2O_2$ (184.2): calcd. C 58.7, H 8.7, N 15.2; found C 58.7, H 8.8, N 15.2.

Pyrazines **3a**, **3b** could be isolated by extraction of the aqueous solution with $CHCl_3$ (cf. ref.[3]).

1-Hydroxy-2-(1-hydroxyethyl)-2,5,5-trimethyl-4-phenyl-3-imidazoline (mixture of two diastereomers, **4**): A solution of 0.4 g (1.6 mmol) of ketone **2a** and 0.2 g of $NaBH_4$ in 10 ml of methanol was stirred for 5 min. and then concentrated. The residue was diluted with 10 ml of saturated brine and extracted with $CHCl_3$ (2 × 20 ml). The combined extracts were dried and evaporated. The residue was treated with hexane, and the precipitate was filtered off to yield 0.38 g (94%) of **4**; m.p. 160–164°C (hexane/ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 1620, 1575 cm^{-1} (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 243 nm (4.05). – ^{1}H NMR (200.13 MHz, CD_3OD): δ = 1.28 (d, *J* = 6.5 Hz, 3H, CH_3CHOH), 1.34 (d, *J* = 6.2 Hz, 3H, CH_3CHOH), 1.41 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.73 (q, *J* = 6.2 Hz, CH_3CHOH), 3.82 (q, *J* = 6.5 Hz, CH_3CHOH), 7.50 (m, 3H), 7.94 (m, 2H, C_6H_5). – $C_{14}H_{20}N_2O_2 \cdot H_2O$ (266.3): calcd. C 63.6, H 8.3, N 10.6; found C 63.4, H 8.6, N 10.4.

2-(1-Hydroxyethyl)-2,5,5-trimethyl-4-phenyl-3-imidazoline-1-oxyl (**8**): A solution of 0.2 g of imidazoline **4** in 5 ml of $CHCl_3$ was stirred with 1 g of MnO_2 for 5 min. Excess oxidant was then filtered off, and the solution was evaporated. Compound **8** was isolated by column chromatography with diethyl ether as the eluent to yield 0.19 g (95%), as an oil. – IR (CCl_4): $\tilde{\nu}$ = 1605 cm^{-1}, 1575 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 246 nm (4.10). EPR ($CHCl_3$): 14.5 G. – $C_{14}H_{19}N_2O_2$ (247.3): calcd. C 68.0, H 7.7, N 11.3; found C 67.7, H 7.8, N 11.3. When the above reaction was

allowed to proceed for 12 h, oxidation of **4** yielded 93% of imidazole **7**, identified by reference to an authentic sample[12].

Hydrazone of 2-Acetyl-1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (**5a**): A solution of 0.3 g (1.2 mmol) of ketone **2a** and 0.5 ml (10 mmol) of hydrazine hydrate in 10 ml of methanol was kept at room temp. for 6 h and then evaporated. The residue was diluted with 10 ml of saturated brine and extracted with $CHCl_3$ (3 × 20 ml). The combined extracts were dried and evaporated. The residue was treated with a mixture of hexane and ethyl acetate 3:1, and the precipitated hydrazone **5a** was filtered off to yield 0.28 g (89%). **5a** was not obtained as an analytically pure sample. – IR (KBr): $\tilde{\nu}$ = 1645 cm^{-1} (C=N), 1605, 1570 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 242 nm (4.09). – ^1H NMR (200.13 MHz, CD_3OD): δ = 1.44 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 7.52 (m, 3H), 7.77 (m, 2H, C_6H_5).

Phenylhydrazone of 2-Acetyl-1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (**5b**): One drop of CH_3COOH was added to a solution of 0.3 g (1.2 mmol) of ketone **2a** and 0.18 ml (1.8 mmol) of phenylhydrazine in 5 ml of methanol and the resulting solution was kept at room temp. for 1 h. The precipitate of phenylhydrazone **5b** was filtered off and washed with 2 ml of methanol to yield 0.35 g (88%), m.p. 203–204°C (ethanol). – IR (KBr): $\tilde{\nu}$ = 1600 cm^{-1}, 1570 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 242 nm (4.13), 270 (4.42). – ^1H NMR (200.13 MHz, CD_3OD): δ = 1.47 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 7.17 (m, 5H, C_6H_5), 7.53 (m, 3H), 7.78 (m, 2H, C_6H_5). – $C_{20}H_{24}N_4O$ (336.4): calcd. C 71.4, H 7.1, N 16.7; found C 71.6, H 7.3, N 16.7.

Semicarbazone of 2-Acetyl-1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (**5c**): A solution of 0.3 g (1.2 mmol) of ketone **2a** and 0.14 g (1.8 mmol) of semicarbazide in 20 ml of methanol was kept at room temp. for 3 h and then evaporated. The residue was treated with water and $CHCl_3$, and the precipitate of **5c** was filtered off and dried to yield 0.18 g (49%), m.p. 191–194°C (ethanol/water). – IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1} (C=O), 1630, 1600, 1570 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 242 nm (4.10). – ^1H NMR (200.13 MHz, CD_3OD): δ = 1.45 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 7.54 (m, 3H), 7.76 (m, 2H, C_6H_5). – $C_{15}H_{21}N_5O_2 \cdot H_2O$ (321.4): calcd. C 56.2, H 7.2, N 21.9; found C 56.0, H 6.9, N 22.1.

Thiosemicarbazone of 2-Acetyl-1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (**5d**): A mixture of 0.3 g (1.2 mmol) of ketone **2a** and 0.14 g (1.6 mmol) of thiosemicarbazide in 15 ml of methanol and 1 drop of CH_3COOH was refluxed for 8 h and then evaporated. The residue was treated with a mixture of 10 ml of sturated brine, 5 ml of hexane and 5 ml of ether, and the precipitate of thiosemicarbazide **5d** was filtered off, washed with hexane, diethyl ether, and water. The yield of crude **5d** was 0.39 g (100%); m.p. 184–185°C (aqueous ethanol). – IR (KBr): $\tilde{\nu}$ = 1640 cm^{-1}, 1620, 1600, 1575 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 240 nm (4.13), 273 (4.32). – ^1H NMR (200.13 MHz, CD_3OD): δ = 1.44 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 7.54 (m, 3H), 7.78 (m, 2H, C_6H_5). – $C_{15}H_{21}N_5OS \cdot H_2O$ (337.4): calcd. C 53.4, H 6.8, N 20.8, S 9.5; found C 53.7, H 6.6, N 21.0, S 9.8.

Semicarbazone of 2-Acetyl-2,5,5-trimethyl-4-phenyl-3-imidazoline-1-oxyl (**9c**): A mixture of 0.1 g of semicarbazone **5c** and 0.5 g of MnO_2 in 5 ml of acetone was stirred at room temp. for 15 min. Excess oxidant was then filtered off, and the solution was evaporated. Nitroxide **9c** was isolated chromatographically, using a mixture of $CHCl_3$ and methanol (30:1) as eluent, to yield 0.09 g (90%); m.p. 202–203°C. – IR (KBr): $\tilde{\nu}$ = 1705 cm^{-1} (C=O), 1595, 1570 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 248 nm (4.34). EPR ($CHCl_3$): 13.9 G. – $C_{15}H_{20}N_5O_2$ (302.4): calcd. C 59.6, H 6.6, N 23.0; found C 59.4, H 6.8, N 22.9.

Oxidation of **5d** for 5 min. under similar conditions afforded 70% of **9d**; m.p. 153–154°C. – IR (KBr): $\tilde{\nu}$ = 1580 cm^{-1} (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 245 nm (4.12), 277 (4.28). – EPR ($CHCl_3$): 14.1 G. – $C_{15}H_{20}N_5OS$ (318.4): calcd. C 56.6, H 6.3, N 22.0, S 10.1; found C 56.6, H 6.5, N 22.0, S 10.3.

1-Hydroxy-4,5-dimethyl-2-phenylimidazole (**13**): A solution of 0.25 g (1 mmol) of ketone **2a**, 0.35 g (5 mmol) of hydroxylamine hydrochloride and 0.16 g (3 mmol) of CH_3ONa in 10 ml of methanol was kept for 20 min. at room temp. and then evaporated. The residue was treated with 5 ml of water and 2 ml of diethyl ether, and the precipitate of imidazole **13** was filtered off and washed with a small amount of diethyl ether, to yield 0.15 g (72%), m.p. 119–121°C (ethyl acetate), 120–122°C for $C_{11}H_{12}N_2O \cdot H_2O$[7], m.p. 180–182°C (DMSO), 180°C for $C_{11}H_{12}N_2O$[7]. – IR (KBr): $\tilde{\nu}$ = 1650 cm^{-1}, 1600 (C=C). – UV (ethanol): λ_{max} (lg ε) = 296 nm (4.30). – ^1H NMR (200.13 MHz, [D$_6$]DMSO): δ = 1.95 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 5.2 (br, 1H, OH), 7.32 (m, 3H), 7.99 (m, 2H, C_6H_5). – ^{13}C NMR (100.61 MHz, [D$_6$]DMSO): δ = 7.16 (CH_3), 11.43 (CH_3), 123.78, 124.62 (C-4,5), 125.62, 127.87, 128.24 (C_6H_5), 135.18 (C-2).

2,3,3a,7-Tetrahydro-2-hydroxy-2,3a,6,6-tetramethyl-5-phenyl-4H-imidazo[2,1-b]isoxazole (**18a**): A solution of 2.0 g (11.2 mmol) of α-hydroxyamino ketone **1a**, 2 ml (19.6 mmol) of acetyl acetone, and 1.7 g (22 mmol) of ammonium acetate in 10 ml of methanol was kept at room temp. for 3 days, diluted with 30 ml of saturated brine, and extracted with $CHCl_3$ (3 × 30 ml). The combined extracts were dried and concentrated. The residue was treated with hexane, and the precipitate of **18a** was filtered off, and washed with a mixture of ether/hexane (1:1). The yield was 1.5 g (52%), m.p. 143–145°C (heptane/ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 1610 cm^{-1}, 1560 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 239 nm (4.05). – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.22 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.41 (d, J = 14 Hz, 1H, CH_2), 2.81 (d, J = 14 Hz, 1H, CH_2), 2.80 (br, 1H, OH), 7.56 (m, 3H), 7.69 (m, 2H, C_6H_5). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 22.18, 25.05, 25.88, 28.82 (4 CH_3), 53.27 (CH_2), 78.02 (C-6), 98.55 (C-3a), 103.54 (C-2), 127.69, 128.25, 130.02, 132.91 (C_6H_5), 175.24 (C-5). – $C_{15}H_{20}N_2O_2$ (260.3): calcd.C 69.2, H 7.7, N 10.8; found C 69.2, H 7.8, N 10.7.

2,3,3a,7-Tetrahydro-2-hydroxy-2,3a,5,6,6-pentamethyl-4H-imidazo-[2,1-b]isoxazole (**18b**): A solution of 1.1 g (10 mmol) of α-hydroxyamino ketone **1b**, 1.5 ml (15 mmol) of acetyl acetone, and 1.5 g (20 mmol) of ammonium acetate in 10 ml of methanol was kept at room temp. for 2 days, diluted with 30 ml of saturated brine, and made alkaline with Na_2CO_3 (to pH 8). The solution was extracted with $CHCl_3$ (3 × 25 ml) and the combined extracts were dried and evaporated. Compound **18b** was isolated chromatographically with a mixture of ethyl acetate and methanol (30:1) as the eluent, to yield 0.8 g (40%) of **18b**; m.p. 98–102°C. – IR (CCl_4): $\tilde{\nu}$ = 1650 cm^{-1} (C=N). – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.20 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2,3a,6,6-CH_3; 1.91 (s, 3H), 1.95 (s, 3H, 5-CH_3), 2.31 (d, J = 13 Hz, 1H, CH_2), 2.40 (s, 1H, CH_2), 2.42 (s, 1H, CH_2), 2.69 (d, J = 13 Hz, 1H, CH_2) (mixture of two diastereomers). – $C_{10}H_{18}N_2O_2$ (198.3): calcd. C 60.8, H 9.1, N 14.1; found C 60.5, H 9.3, N 13.8.

Reaction of α-Hydroxyamino Ketone **1c** *with Acetyl Acetone:* A solution of 1.4 g (10 mmol) of α-hydroxyamino ketone **1c**, 1.5 ml

(15 mmol) of acetyl acetone, and 1.5 g (20 mmol) of ammonium acetate in 10 ml of methanol was kept at room temp. for 24 h and evaporated. The residue was dissolved in 10 ml of saturated brine and extracted with $CHCl_3$ (4 × 25 ml). The combined extracts were dried and evaporated, and the residue was treated with a 1:3 diethyl ether/hexane mixture. The precipitate of pyrazine **19** was filtered off, and washed with hexane. 2 g of MnO_2 was added to the filtrate and the mixture was stirred for 10 hours at room temp. Excess oxidant was then filtered off, the solution was evaporated, and nitroxide **16c** was isolated chromatographically with ethyl acetate as the eluent.

19: Yield 0.8 g (64%), m.p. 270–272°C (ethanol). – IR (KBr): $\tilde{\nu}$ = 1575 cm^{-1} (C=N). – UV (ethanol): λ_{max} (lg ε) = 234 nm (4.15). ^1H NMR (200.13 MHz, CD_3OD): δ = 1.54 (m, 2H), 2.28 (m, 2H), 2.74 (m, 2H), 3.67 (m, 2H), 1.86 (s, 6H, 2 CH_3). – $C_{14}H_{22}N_2O_2$ (250.3): calcd. C 67.2, H 8.8, N 11.2; found C 67.4, H 9.0, N 11.4.

16c: Yield 0.35 g (16%), oil. – IR (CCl_4): $\tilde{\nu}$ = 1740 cm^{-1}, 1720, 1710 (C=O), 1645 (C=N). – EPR ($CHCl_3$): 14.1 G. – $C_{12}H_{19}N_2O_2$ (223.3): calcd. C 64.6, H 8.5, N 12.6; found C 64.9, H 8.3, N 12.5.

Oxidation of Semiacetals **18a**, **18b**: A solution of 0.2 g of **18a**, **18b** in 10 ml of $CHCl_3$ was stirred with 1 g of MnO_2 for 5 h at room temp. Excess oxidant was filtered off, and the solution was evaporated.

16a: Yield 0.2 g (≈100%), m.p. 60–61°C (hexane). – IR (KBr): $\tilde{\nu}$ = 1720 cm^{-1} (C=O), 1605, 1575 (C=C, C=N). – IR (CCl_4): $\tilde{\nu}$ = 1720 cm^{-1}, 1705 (C=O), 1595, 1560 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 247 nm (4.04). – EPR ($CHCl_3$): 14.0 G. – $C_{15}H_{19}N_2O_2$ (259.3): calcd. C 69.5, H 7.3, N 10.8; found C 69.7, H 7.4, N 10.8.

16b: Yield 0.2 g (≈100%), oil (purified chromatographically with a mixture of $CHCl_3$/methanol, 30:1). – IR (CCl_4): $\tilde{\nu}$ = 1725 cm^{-1}, 1710 (C=O), 1645 (C=N). – EPR ($CHCl_3$): 14.2 G. – $C_{10}H_{17}N_2O_2$ (197.3): calcd. C 61.0, H 8.6, N 14.2; found C 60.9, H 8.8, N 13.9.

2-(2-Hydroxyaminopropyl)-2,5,5-trimethyl-4-phenyl-3-imidazoline-1-oxyl (**15**): A solution of 0.4 g (1.55 mmol) of ketone **16a**, 0.13 g (1.85 mmol) of hydroxylamine hydrochloride and 0.08 g (1.55 mmol) of CH_3ONa in 10 ml of methanol was kept for 1 h and then evaporated. The residue was treated with 5 ml of water, and the precipitated oxime **15** was filtered off; yield 0.37 g (87%); m.p. 121–123°C (heptane/ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 1650 cm^{-1}, 1595, 1570 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 246 nm (4.16). – EPR ($CHCl_3$): 14.3 G. – $C_{15}H_{20}N_3O_2$ (274.3): calcd. C 65.6, H 7.3, N 15.3; found C 65.8, H 7.5, N 15.1.

2-(2-Hydroxypropyl)-2,5,5-trimethyl-4-phenyl-3-imidazoline-1-oxyl (**17**): A mixture of 0.4 g (1.5 mmol) of acetal **18a** and 0.2 g (5.3 mmol) of $NaBH_4$ in 10 ml of ethanol was stirred at room temp. for 12 h and then evaporated. The residue was diluted with 10 ml of water and extracted with $CHCl_3$ (2 × 20 ml). The extract was dried, $MgSO_4$ was filtered off, and 0.5 g of MnO_2 was added to the filtrate. After stirring at room temp. for 10 min., excess oxidant was filtered off, and the solution was evaporated. **17** was isolated chromatographically with $CHCl_3$ as the eluent, yielding 0.4 g (≈ 100%); m.p. 63–65°C. – IR (CCl_4): $\tilde{\nu}$ = 3460 cm^{-1} (OH), 1600, 1560 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 247 nm (4.16). – EPR ($CHCl_3$): 14.5 G. – $C_{15}H_{21}N_2O_2$ (261.3): calcd. C 69.0, H 8.0, N 10.7; found C 69.2, H 8.2, N 10.7.

3a,7-Dihydro-2,3a,6,6-tetramethyl-4H-imidazo[2,1-b]isoxazole (**20**): A solution of 0.3 g of hemiacetal **18a** and 0.01 g of TsOH in 10 ml of benzene was refluxed for 1 h, and then evaporated. The residue was dissolved in 10 ml of $CHCl_3$, washed with a 2% aqueous solution of Na_2CO_3, dried, and evaporated. **20** was isolated by thin-layer chromatography on silica gel using a 1:3 ethyl acetate/hexane mixture as eluent, yielding 0.24 g (86%), as an oil. – IR (CCl_4): $\tilde{\nu}$ = 1675 cm^{-1}, 1605, 1565 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 241 nm (4.20). – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.50 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.72 (d, J = 1 Hz, 3H, 2-CH_3), 4.78 (q, J = 1 Hz, 1H, CH=), 7.34 (m, 3H), 7.69 (m, 2H, C_6H_5). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 11.23, 21.90, 26.73, 28.79 (4 CH_3), 77.02 (C-6), 99.31 (C-3), 102.15 (C-3a), 127.89, 128.09, 129.77, 132.74 (C_6H_5), 152.73 (C-5), 172.11 (C-2). – $C_{15}H_{18}N_2O$ (242.3): calcd. C 74.4, H 7.4, N 11.6; found C 74.1, H 7.4, N 11.3.

2,3,3a,7-Tetrahydro-3a,6,6-trimethyl-2-oxo-5-phenyl-4H-imidazo[2,1-b]isoxazole (**21a**): A solution of 1.8 g (10 mmol) of α-hydroxyamino ketone **1a**, 1.9 ml (15 mmol) of acetoacetic ester, and 1.6 g (21 mmol) of ammonium acetate in 10 ml of methanol was kept at room temp. for 12 h and then evaporated. The residue was taken up in 10 ml of water, and the solution was extracted with $CHCl_3$. The combined extracts were dried and evaporated, and **21a** was isolated chromatographically with $CHCl_3$ as the eluent, yielding 0.8 g (33%); m.p. 149–150°C (heptane/ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 1790 cm^{-1} (C=O), 1610, 1575 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 244 nm (4.19). – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.59 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 3.05 (d, J = 18 Hz, 1H, $-CH_2-$), 3.27 (d, J = 18 Hz, 1H, $-CH_2-$), 7.40 (m, 3H), 7.72 (m, 2H, C_6H_5). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 22.50, 25.61, 27.62 (3 CH_3), 42.20 (CH_2), 78.22 (C-6), 96.82 (C-3a), 128.03, 128.42, 130.73, 131.47 (C_6H_5), 171.99, 173.69 (C=O, C=N). – $C_{14}H_{16}N_2O_2$ (244.3): calcd. C 68.9, H 6.6, N 11.5; found C 69.1, H 6.8, N 11.4.

Similarly **21b** was obtained from α-hydroxyamino ketone **1b**, in a yield of 59% as an oil. – IR (CCl_4): $\tilde{\nu}$ = 1790 cm^{-1} (C=O), 1650 (C=N). – ^1H NMR (200.13 MHz, CD_3OD): δ = 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.11 (s, 3H, 5-CH_3), 3.08 (d, J = 18 Hz, 1H, $-CH_2-$), 3.24 (d, J = 18 Hz, 1H, $-CH_2-$). – $C_9H_{14}N_2O_2$ (182.2): calcd. C 59.4, H 7.7, N 15.4; found C 59.7, H 7.5, N 15.1.

2,3,3a,7-Tetrahydro-3a,6-dimethyl-5,6-tetramethylene-4H-imidazo[2,1-b]isoxazole (**21c**): A solution of 1.3 g (9 mmol) of α-hydroxyamino ketone **1c**, 1.7 ml (13.7 mmol) of acetoacetic ester, and 1.5 g (18 mmol) of ammonium acetate in 10 ml of methanol was kept at room temp. for 24 h. It was then diluted with 20 ml of saturated brine, made alkaline with Na_2CO_3 (to pH 8), and extracted with $CHCl_3$ (3 × 30 ml). The pooled extracts were dried and evaporated, and the residue was treated with a 1:1 mixture of ether/hexane. The precipitated pyrazine **19** was filtered off, affording 0.6 g (53%). The filtrate was evaporated, and lactone **21c** was isolated chromatographically with diethyl ether as eluent, to yield 0.5 g (26%) of **21c** as an oil. – IR (CCl_4): $\tilde{\nu}$ = 1785 cm^{-1} (C=O), 1650 (C=N). – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.15 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.1–2.4 [m, 8H, $(CH_2)_4$], 2.68 (s, 1H, CH_2), 2.71 (s, 1H, CH_2), 2.82 (d, J = 18 Hz, 1H, CH_2), 2.94 (d, J = 18 Hz, 1H, CH_2) (mixture of two diastereomers, 1:1). – $C_{11}H_{16}N_2O_2$ (208.3): calcd. C 63.4, H 7.7, N 13.5; found C 63.2, H 7.3, N 13.5.

2-(1,1-Dimethyl-2-oxopropyl)-5-methyl-4-isoxazoline-3-one (**22**): A solution of 2.3 g (20 mmol) of α-hydroxyamino ketone **1b**, 3.8 ml (30 mmol) of acetoacetic ester, and 1.6 g (30 mmol) of CH_3ONa in 20 ml of methanol was kept at room temp. for 7 days and then evaporated. Compound **22** was isolated chromatographically with $CHCl_3$ as the eluent to yield 0.6 g (17%); m.p. 52–53°C (diethyl

ether). – IR (CCl_4): $\tilde{\nu}$ = 1775 cm^{-1}, 1730 (C=O), 1610 (C=C). – UV (ethanol): λ_{max} (lg ε) = 266 nm (4.11). – ^1H NMR (200.13 MHz, $CDCl_3$): δ = 1.37 (s, 6H, 2 CH_3), 2.07 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 4.96 (s, 1H, CH=). – $C_9H_{13}NO_3$ (183.2): calcd. C 59.3, H 6.6, N 7.7; found C 59.0, H 6.5, N 7.7.

Reaction of **21a** *with* $NaBH_4$: A solution of 0.4 g (1.6 mmol) of **21a** and 0.1 g (2.6 mmol) of $NaBH_4$ in 20 ml of ethanol was kept at room temp. for 2 h and then evaporated. The residue was diluted with 10 ml of water and extracted with $CHCl_3$ (3 × 15 ml). The pooled extracts were dried, the solvent was evaporated, and the residue was treated with hexane. The precipitate formed was filtered off and dissolved in 20 ml of $CHCl_3$, and 1 g of MnO_2 was added. After stirring at room temp. for 1 h, excess oxidant was filtered off, and the solution was evaporated. Aldehyde **24** and alcohol **23** were isolated chromatographically using a 3:1 mixture of hexane/ethyl acetate as the eluent.

23: Yield 0.15 g (38%), oil. – IR (CCl_4): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 1595, 1560 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 247 nm (4.23). – EPR ($CHCl_3$): 14.6 G. – $C_{14}H_{19}N_2O_2$ (247.3): calcd. C 68.2, H 7.7, N 11.3; found C 68.4, H 7.9, N 11.2.

24: Yield 0.11 g (28%), oil. – IR (CCl_4): $\tilde{\nu}$ = 1725 cm^{-1} (C=O), 1600, 1570 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 246 nm (4.10). – EPR ($CHCl_3$): 14.2 G. – $C_{14}H_{17}N_2O_2$ (245.3): calcd. C 68.6, H 6.9, N 11.4; found C 68.9, H 7.1, N 11.2.

2-Methoxycarbonylmethyl-2,5,5-trimethyl-4-phenyl-3-imidazoline-1-oxyl (**25a**): A solution of 0.2 g of lactone **21a** in a mixture of 2 ml of methanol and 2 ml of 5% aqueous NaOH solution was kept at room temp. for 1 h, acidified with 5% HCl to pH 3 and extracted with $CHCl_3$. The pooled extracts were dried and filtered, 2 g of MnO_2 was added to the filtrate and the mixture was stirred for 10 min. Excess oxidant was then filtered off, and the filtrate was concentrated by evaporation. The residue was dissolved in 10 ml of diethyl ether and extracted with 2% aqueous NaOH (3 × 5 ml). The combined aqueous extracts were washed with ether (2 × 5 ml), acidified to pH 3, and extracted with diethyl ether (3 × 10 ml). The organic extract was dried and filtered and the filtrate was treated with an ethereal solution of diazomethane, obtained from 0.3 g of nitrosomethylurea, and evaporated. Ester **25a** was isolated chromatographically, with $CHCl_3$ as the eluent, to give 0.15 g (66%) as an oil. – IR (CCl_4): $\tilde{\nu}$ = 1755 cm^{-1} (C=O), 1610, 1585 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 243 nm (4.20). – EPR ($CHCl_3$): 14.3 G. – $C_{15}H_{19}N_2O_3$ (275.3): calcd. C 65.5, H 6.9, N 10.2; found C 65.3, H 7.2, N 10.0.

2-Carbamoylmethyl-2,5,5-trimethyl-4-phenyl-3-imidazoline-1-oxyl (**25b**): A mixture of 0.3 g of lactone **21a**, 10 ml of methanol, and 2 ml of aqueous 25% NH_3 was stirred at room temp. for 3 days. The methanol was then evaporated and the residue was treated with 5 ml of saturated brine. The precipitate was filtered off and dried in air. Amide **25b** was purified chromatographically with a mixture of $CHCl_3$/methanol (30:1) as the eluent, to yield 0.25 g (78%); m.p. 143–145°C (heptane/ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3410 cm^{-1}, 3190, 1700, 1640 ($CONH_2$), 1605, 1575 (C=C, C=N). – UV (ethanol): λ_{max} (lg ε) = 246 nm (4.18). – EPR ($CHCl_3$): 13.6 G. – $C_{14}H_{18}N_3O_2$ (260.3): calcd. C 64.6, H 6.9, N 16.2; found C 64.3, H 7.0, N 15.9.

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