Ammonium acetate as a catalyst of the condensation of sterically hindered functionalized hydroxylamines with ketones

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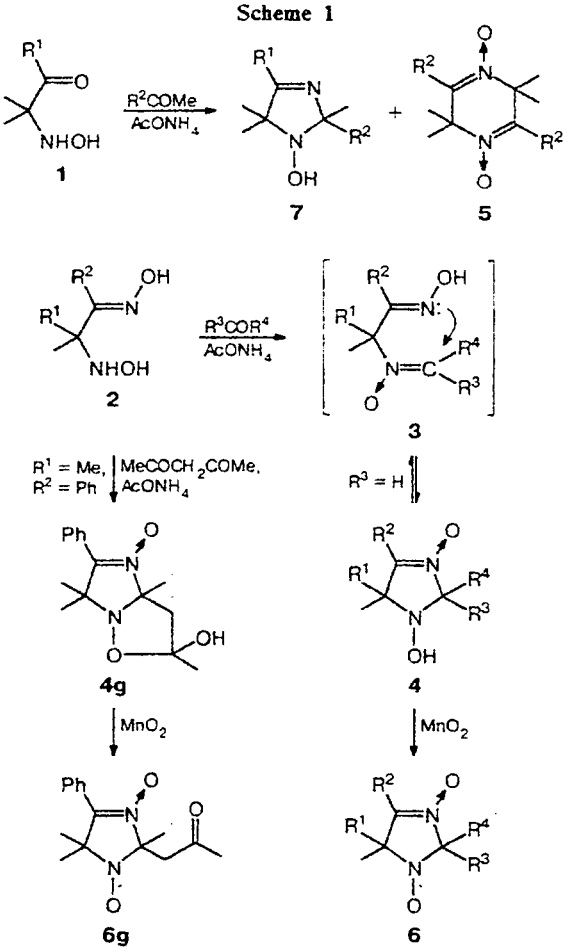
Ammonium acetate was found to be a catalyst of the condensation of α-hydroxylamino oximes and α-hydroxylamino alcohols with ketones. This condensation leads to sterically hindered heterocyclic hydroxylamines, which are precursors of stable nitroxides.

Key words: hydroxylamines; 3-imidazoline-3-oxides; oxazolidines; stable nitroxyl radicals.

Stable nitroxyl radicals of the 3-imidazoline and 3-imidazoline-3-oxide series are of great interest due to the possibility of functionalizing them, *e.g.*, for the synthesis of spin labels, sounds and chelating reagents.[1] The method of synthesis of these nitroxyl radicals is based on condensation of α-hydroxylamino ketones (**1**) with ketones in the presence of ammonium acetate or of α-hydroxylamino oximes (**2**) with acetone or its diethyl ketal.[1] The interaction of α-hydroxylamino oximes with acetone occurs only in the presence of an acid as a catalyst, the rate being low.[2] The first stage of this reaction is believed to be formation of nitron (**3**), which further cyclizes into the end product, 3-imidazoline-3-oxide (**4**)[3] (Scheme 1). Apparently, the cyclization cannot be a limiting stage of the entire process because in some cases, when the substituent R^3 = H, a tautomeric equilibrium between the cyclic 3-imidazoline-3-oxide and acyclic nitron-oxime structures (**3** ⇌ **4**) is observed.[4,5] In connection with this, such a considerable difference in reactivity of α-hydroxylamino ketones and α-hydroxylamino oximes with respect to ketones appears strange, especially as the reactions of these compounds with aldehydes proceed under the same conditions with comparable rates.[4–7] It should also be noted that the formation of side products, derivatives of dihydropyrazine-1,4-dioxide (**5**), is observed upon the interaction of α-hydroxylamino ketones with ketones and $AcONH_4$, whereas heating the solutions of both free bases, α-hydroxylamino ketones **1**, and their hydrochlorides in the absence of $AcONH_4$ practically does not result in the formation of derivatives of pyrazine dioxide.[8]

Based on these data, one could assume that ammonium acetate is a catalyst of the condensation with *N*-substituted hydroxylamines and ketones involved. In the present work, this assumption was confirmed experimentally. The reaction of hydroxylamino oximes with ketones (see Scheme 1) was carried out by boiling under reflux in MeOH in the presence of $AcONH_4$ (Table 1).

Scheme 1



2: R^1 = Me, R^2 = Ph (**a**), Et (**b**), H (**c**); $R^1 + R^2 = (CH_2)_5$ (**d**)

The oxidation of 1-hydroxy-3-imidazoline-3-oxides **4** with magnesium dioxide results in nitroxyl radicals **6** in quantitative yields.

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Table 1. The interaction of hydroxylamino oximes with ketones

Product	R^1	R^2	R^3	R^4	*t* /h	Yield (%)
4a	Me	Ph	Me	Me	2	80[a]
4b	Me	Ph	Me	C_6H_{13}	4	70
4c	Me	Ph	$(CH_2)_5$		1	95
4d	Me	Ph	Me	$(CH_2)_2CO_2Me$	4	50
4e	Me	Ph	Me	$C_{17}H_{35}$	6	70
4f	Me	Et	Me	Me	3	80[b]
4g	Me	Ph	Me	CH_2COCH_2[c]	2	60
4h	$(CH_2)_4$		Me	Me	2	80

[a] In carrying out the reaction with acetone in the presence of dilute HCl, the yield after 50 h amounts to 52% (see Ref. 2).
[b] Upon oxidation into the corresponding radical (**6f**).
[c] The condensation product exists as a bicyclic semiacetal structure **4g**, whose oxidation results in radical **6g**.

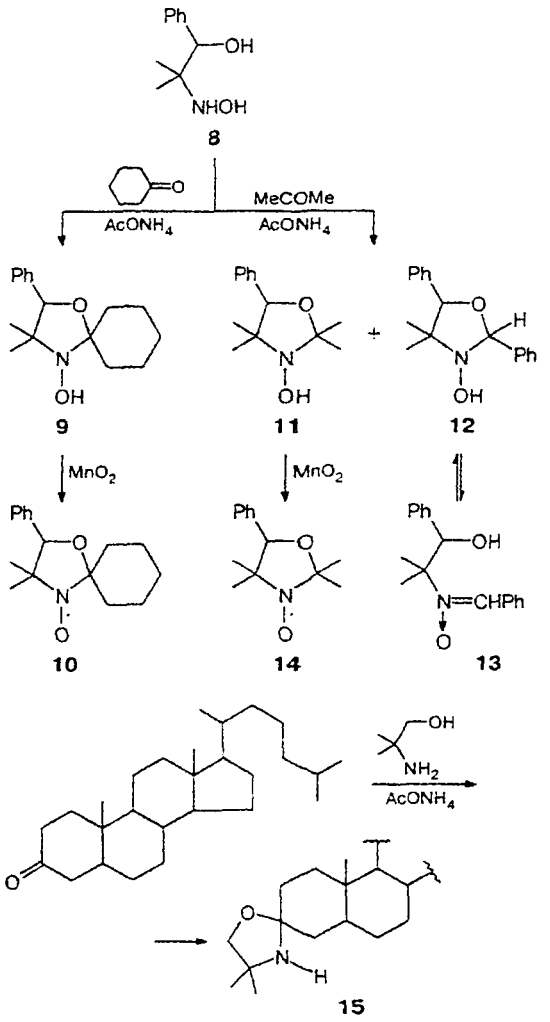
The condensation of compounds **1** and **2** with ketones in the presence of ammonium acetate is reversible. In the case of 3-imidazoline-3-oxides, the equilibrium is shifted to the reaction product more strongly than in the case of derivatives of 3-imidazoline because of the greater hydrolytic lability of the latter. Thus, upon dissolution of 1-hydroxy-3-imidazoline **7** ($R^1 = R^2 = Me$) in 80% AcOH, hydrolytic ring-disclosure of the heterocycle occurs immediately to give α-hydroxylamino ketone **1** ($R^1 = Me$). Because of this, α-hydroxylamino oximes **2** react with ketones in higher (as a rule) yields of condensation products than those resulting from the condensation of α-hydroxylamino ketone **1**, though the reactivities of these compounds are close under the conditions involved.

It is noteworthy that an attempt to carry out the condensation of hydroxylamino oximes **2a** with triacetoneamine under similar conditions led to compound **4a**, a product of condensation with acetone, due to the ease of hydrolytic splitting of the piperidine ring. The product of the condensation of α-hydroxylamino oximes **2c** with acetone was not isolated, and, in this case, dihydropyrazine-1,4-dioxide **5** ($R^2 = H$) was a reaction product.

Usually, nitroxyl radicals of the oxazolidine series (doxyls) can be obtained by condensation of α-amino alcohols with ketones with subsequent oxidation with *m*-chloroperbenzoic acid.[9] In part, this is due to the better availability of α-amino alcohols compared to α-hydroxylamino alcohols and due to the fact that the latter do not react with ketones under similar conditions, probably because of their lower stability. The addition of ammonium acetate allows one to perform the condensation of α-hydroxylamino alcohols with ketones.

Thus, the interaction of α-hydroxylamino alcohol **8** with cyclohexanone in the presence of $AcONH_4$ is completed after 2 h to give oxazolidine **9** (yield 80%), which is oxidized with magnesium dioxide or simply air

Scheme 2



oxygen to doxyl **10** in quantitative yield. Earlier, such yields of doxyl radicals were not usually attained with the use of α-amino alcohol as a acyclic precursor, first, due to the moderate yield of the condensation product, and, second, because of possible oxidation of doxyl formed to an oxaammonium salt followed by the ring-opening of the heterocycle.[10] The yield of the condensation product is also reduced by the low stability of α-hydroxylamino alcohols, which readily undergo cleavage of the C—C bond. In the case of compound **8**, this results in the formation of benzaldehyde as a reaction product (*cf.* Ref. 7). Hence, when the duration of interaction of α-hydroxylamino alcohol **8** with acetone is extended (>2 h), oxazolidine **12** is accumulated along with tetramethyl-substituted 1-hydroxyoxazolidine **11** formed initially. According to ^1H NMR ($CDCl_3$) data, compound **12** exists in an acyclic tautomeric form **13** (*cf.* Ref. 11). However, it should be noted that the typical conditions of the condensation of 2-aminoisobutyl alcohol with ketones are much more drastic (many-

hours refluxing in toluene with separation of water formed) than is required for carrying out the reaction with α-hydroxylamino alcohol. 1-Hydroxyoxazolidine **11** is oxidized in nitroxyl radical **14** under very mild conditions (under the action of MnO_2 or air oxygen) in quantitative yield.

Ammonium acetate seems to accelerate the condensation of 2-amino-2-methylpropanol with ketones as well. Thus, when a solution of 5α-cholestan-3-one is refluxed with a threefold excess of 2-amino-2-methylpropanol in the presence of $AcONH_4$, the conversion of this compound amounts after 2 h to 70% (according to ^1H NMR spectroscopy data). One of epimers is a predominant product of the condensation, which is evidenced by the signals of the $O—CH_2—$ group (δ 3.45 and 3.27) included in the heterocycle of oxazolidine **15** (in the ~50 : 1 ratio, *cf.* Ref. 15). In the absence of $AcONH_4$, this reaction does not proceed with a marked rate under the conditions mentioned.

Probably, the catalytic effect of ammonium acetate can be explained by the formation of ketone imine at the first stage of the reaction, whose protonated form is likely more reactive in relation to a nucleophilic attack from the part of the hydroxylamino group. One can postulate that nitron **3** does not result from the interaction of hydroxylamino oxime **2** with ketones, while an intramolecular substitution of the nitrogen atom of the oxime group for the protonated amino group takes place to give the end reaction product, 3-imidazoline-3-oxide **4**.

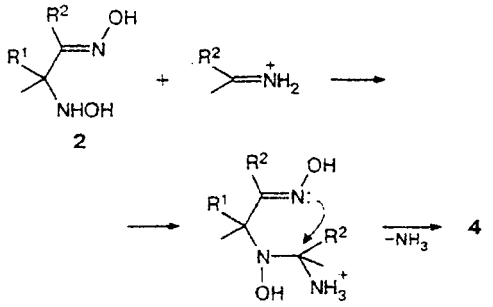


Table 2. The characteristics of compounds synthesized

Compound	M.p. /°C [a]	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (log ε)	Found / Calculated (%) C	H	N	Molecular formula
4b	112—114	1555, 1575 (C=N)	287 (4.00)	70.9 / 71.2	9.2 / 9.2	9.2 / 9.2	$C_{18}H_{28}N_2O_2$
4d	151—153	1745 (C=O); 1555, 1575 (C=N)	286 (3.95)	60.4 / 60.2	7.7 / 7.7	9.6 / 9.8	$C_{16}H_{22}N_2O_4$
4e	40—42	1550, 1575 (C=N)	286 (3.94)	76.1 / 76.0	10.8 / 10.9	6.1 / 6.1	$C_{29}H_{50}N_2O_2$
4g	138—142 [b]	1545, 1575, 1585 (C=N)	285 (3.98)	65.3 / 65.3	7.4 / 7.3	10.1 / 10.1	$C_{15}H_{20}N_2O_3$
6b	— [c]	1535, 1570 (C=N)[d]	286 (4.02)	71.1 / 71.3	8.8 / 8.9	9.0 / 9.2	$C_{18}H_{27}N_2O_2$
6d	96—98	1740 (C=O); 1535, 1570 (C=N)	286 (4.11)	60.3 / 60.4	7.6 / 7.4	9.7 / 9.8	$C_{16}H_{21}N_2O_4$
6e	30—32	1540, 1575 (C=N)[d]	287 (4.08)	76.2 / 76.2	11.0 / 10.7	6.0 / 6.1	$C_{29}H_{49}N_2O_2$
6g	117—118	1715 (C=O); 1545, 1580 (C=N)	288 (4.04)	65.5 / 65.5	7.1 / 6.9	10.1 / 10.2	$C_{15}H_{19}N_2O_3$
9	161—163	1600 (Ph)	—	74.2 / 73.8	8.7 / 8.5	5.3 / 5.4	$C_{16}H_{22}NO_2$
10	100—101	1100 (C—O); 1600 (Ph)	—	74.6 / 74.2	8.3 / 8.1	5.2 / 5.4	$C_{16}H_{22}NO_2$
11	106—107	—	—	70.5 / 70.7	8.8 / 8.6	6.3 / 6.3	$C_{13}H_{19}NO_2$
14	— [c]	—	—	70.5 / 70.9	8.0 / 8.2	6.1 / 6.4	$C_{13}H_{18}NO_2$

[a] Compounds obtained were purified by recrystallization from: a hexane—ethyl acetate mixture (**4b**,**g**, and **6g**), ethyl acetate (**4d**), methanol (**4e** and **6e**), ethanol (**9**), hexane (**6d** and **11**); **6b** and **14** were purified by chromatographing on a column (silica gel, a $CHCl_3$—hexane, 1 : 1). Data of compound **10** from elemental analysis are satisfactory without additional purification.

[b] A mixture of diastereomers. [c] Oil. [d] The spectrum was recorded in CCl_4.

Experimental

The IR spectra were recorded on a Specord M-80 spectrometer in KBr (0.25%) and in CCl_4 (5%). The UV spectra were recorded on a Specord UV-VIS spectrometer in EtOH. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument at 300 K (solution concentrations were 5%), and the chemical shift values were determined with reference to the solvent signal. The identity of the compounds to the authentic samples was determined by comparing their IR and UV spectra, melting points, and TLC data (Silufol UV-254, $CHCl_3$—MeOH). The characteristics of the compounds synthesized are given in Table 2.

Syntheses of 3-imidazoline-3-oxides 4a—g.

1-Hydroxy-2,2,5,5-tetramethyl-4-phenyl-3-imidazoline-3-oxide (4a). A solution of α-hydroxylamino oxime **2a** (1 g, 5 mmol) and ammonium acetate (0.6 g, 1.5 mmol) in 10 mL of acetone and 5 mL of methanol was refluxed for 2 h and concentrated. The residue was treated with 10 mL of water, and the precipitate was filtered off, washed with water, and dried. Compound **4a** (0.97 g) was obtained with m.p. 192—193 °C (from ethyl acetate) (*cf.* Ref. 12: m.p. 193—194 °C).

The reaction of α-hydroxylamino oximes **2b—d** with acetone was carried out under similar conditions. To obtain imidazoline **4h**, the reaction mixture was concentrated, and the residue was diluted with 5 mL of a saturated aqueous NaCl solution and with 5 mL of hexane. The precipitate that formed was filtered off and washed with hexane and a mixture of ether with hexane (1 : 1). Compound **4h** was obtained with m.p. 172—174 °C (from ethyl acetate) (*cf.* Ref. 12: m.p. 172—174 °C).

In the case of hydroxylamino oxime **2b**, the solution was concentrated, and the residue was diluted with 20 mL of acetone and dried with anhydrous Na_2CO_3 for 30 min. The precipitate of inorganic salts was filtered off, and MnO_2 (2 g) was added to the filtrate and stirred at 20 °C for 30 min. The excess oxidant was filtered off, and the solution was concentrated. Radical **6f** was isolated by column chromatography (silica gel, $CHCl_3$), m.p. 91—93 °C (*cf.* Ref. 13: m.p. 93—94 °C).*

2-Hexyl-1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline-3-oxide (4b). A solution of hydroxylamino oxime **2a** (0.97 g, 5 mmol), methyl hexyl ketone (1.95 mL, 12.5 mmol), and ammonium acetate (0.77 g, 10 mmol) in 7 mL of MeOH was refluxed for 4 h and concentrated. The residue was diluted with 10 mL of a saturated aqueous NaCl solution and extracted with $CHCl_3$ (3×15 mL). The extract was washed with 1% HCl, dried with $MgSO_4$, and the solution was concentrated. The residue was crystallized by adding a small amount of pentane. The precipitate was filtered off to give imidazoline **4b** (1.1 g). ^1H NMR ($CDCl_3$), δ: 0.84 (m, 3 H, 2-C_6H_{13}); 1.24 (m, 8 H, 2-C_6H_{13}); 1.95 (m, 2 H, 2-C_6H_{13}); 1.40 (s, 3 H, 2-Me); 1.58 (s, 6 H, 5,5-Me_2); 5.62 (br.s, 1 H, OH); 7.40 (m, 3 H, Ph); 8.0 (m, 2 H, Ph).

The reactions of hydroxylamino oxime **2a** with cyclohexanone, methyl levulinate, methyl heptadecyl ketone, and acetyl acetone were carried out under similar conditions. In all cases, the reaction mixture was concentrated and then diluted with 10 mL of a saturated aqueous NaCl solution. In the case of imidazoline **4c**, the solution was acidified until pH 3 with 1% HCl; 10 mL of hexane was added, and the precipitate of imidazoline **4c** was filtered off, m.p. 178—180 °C (from EtOH) (*cf.* Ref. 14: m.p. 178—180 °C).

To separate imidazoline **4e**, the solution was extracted with ether (3×15 mL), and the extract was washed with 1% HCl and dried with $MgSO_4$. The solution was concentrated and chromatographed on a column (silica gel; hexane—$CHCl_3$, 2 : 1). Imidazoline **4e** was isolated; ^1H NMR ($CDCl_3$), δ: 0.85 (m, 3 H, 2-$C_{17}H_{35}$); 1.22 (m, 30 H, 2-$C_{17}H_{35}$); 1.96 (m, 2 H, 2-$C_{17}H_{35}$); 1.40 (s, 3 H, 2-Me); 1.58 (s, 6 H, 5,5-Me_2); 6.10 (br.s, 1 H, OH); 7.38 (m, 3 H, Ph); 8.02 (m, 2 H, Ph).

Imidazoline **4d** was extracted with $CHCl_3$ (3×15 mL), and the extract was washed with 1% HCl and dried with $MgSO_4$. The solution was concentrated, and the residue was crystallized by rubbing with ether. The precipitate of compound **4d** was filtered off and washed with ether. ^1H NMR ($CDCl_3$), δ: 1.31 (s, 3 H, 2-Me); 1.58 (s, 3 H, 5-Me); 1.60 (s, 3 H, 5-Me); 2.10—2.50 (m, 4 H, —$(CH_2)_2$—); 3.59 (s, 3 H, OMe); 5.13 (br.s, 1 H, OH); 7.39 (m, 3 H, Ph); 8.08 (m, 2 H, Ph).

Imidazoline **4g** was extracted with $CHCl_3$ and chromatographed on a column (silica gel, ethyl acetate). ^1H NMR ($CDCl_3$), δ: 1.33 (s, 3 H); 1.38 (s, 3 H); 1.45 (s, 3 H); 1.50 (s, 3 H); 1.53 (s, 3 H); 1.59 (s, 3 H); 1.66 (s, 3 H); 1.72 (s, 3 H); 2.06 (d, 1 H, J = 13.5 Hz); 2.36 (d, 1 H, J = 14.5 Hz); 3.14 (d, 1 H, J = 14.5 Hz); 3.17 (d, 1 H, —CH_2—, J = 13.5 Hz); 7.34 (m, 3 H); 7.80 (m, 2 H, Ph), a mixture of two diastereomers (3 : 7).

The reaction of hydroxylamino oxime **2a** with triacetoneamine under similar conditions results after 4 h in imidazoline **4a**, yield 75%.

Syntheses of oxazolidines 9 and 11.

3-Hydroxy-4,4-dimethyl-5-phenyloxazolidine-2-spirocyclohexane (9) was synthesized by the reaction of hydroxylamino alcohol **8** with cyclohexanone under similar conditions (the duration of the reaction was 2 h). After the reaction mixture was cooled, a precipitate of oxazolidine **9** was formed, which was filtered off and washed with a small amount of cooled MeOH. Yield 80%. ^1H NMR ($CDCl_3$), δ: 0.82, 1.31 (both s, 3 H each, 4,4-Me_2); 1.7 (m, 10 H, $(CH_2)_5$); 4.69 (s, 1 H, 5-H); 7.38 (m, 5 H, Ph).

3-Hydroxy-2,2,4,4-tetramethyl-5-phenyloxazolidine (11) was synthesized by the reaction of hydroxylamino alcohol **8** with acetone under the conditions indicated for hydroxylamino oxime **2a** (the duration of the reaction was 2 h). The solution was concentrated, and the residue was diluted with 10 mL of a saturated aqueous NaCl solution. The precipitate was filtered off and dried. Oxazolidine **11** was isolated by column chromatography (silica gel, $CHCl_3$) in a 75% yield. When the reaction was carried out for 4 h, the sole product isolated was hydroxynitron **13**, yield 30%, m.p. 127—129 °C (from hexane) (*cf.* Ref. 11: m.p. 126—128 °C). ^1H NMR ($CDCl_3$), δ: 1.48 (s, 3 H, 4-Me); 1.70 (s, 3 H, 4-Me); 4.86 (d, 1 H, C<u>H</u>OH, J = 6 Hz); 6.24 (d, 1 H, CHO<u>H</u>, J = 6 Hz); 7.30 (m, 10 H, 2,5-Ph_2).

Synthesis of nitroxyl radicals 6b,d,e,g, 10, and 14 (general procedure). A solution of imidazoline **4b,d,e,g** or oxazolidine **9** or **11** (0.2 g) in 10 mL of $CHCl_3$ was stirred with MnO_2 (0.5 g) for 20 min (in the case of compound **4g**, for 12 h). The excess of the oxidant was filtered off, and the solution was concentrated to obtain the corresponding nitroxyl radical. The yields of **6b,d** were 95% and of **6e,g**, **10**, and **14** were ~100%.

The interaction of 5α-cholestan-3-one with 2-amino-2-methylpropanol. A solution of 5α-cholestan-3-one (0.39 g, 1 mmol), 2-amino-2-methylpropanol (0.29 g, 3 mmol), and ammonium acetate (0.08 g, 1 mmol) in 3 mL of MeOH was refluxed for 2 h and cooled to 0 °C. The precipitate that

* The oxidation of 1 hydroxyderivative of 3-imidazoline-3-oxide **4f** into a nitroxyl radical **6f** was performed because the isolation of compound **4f** is difficult.

formed was filtered off, and oxazoline **15** (0.39 g) was obtained.

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