4-Hydroxyiminonitromethyl-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl as a precursor of spin-labeled nitrile oxide

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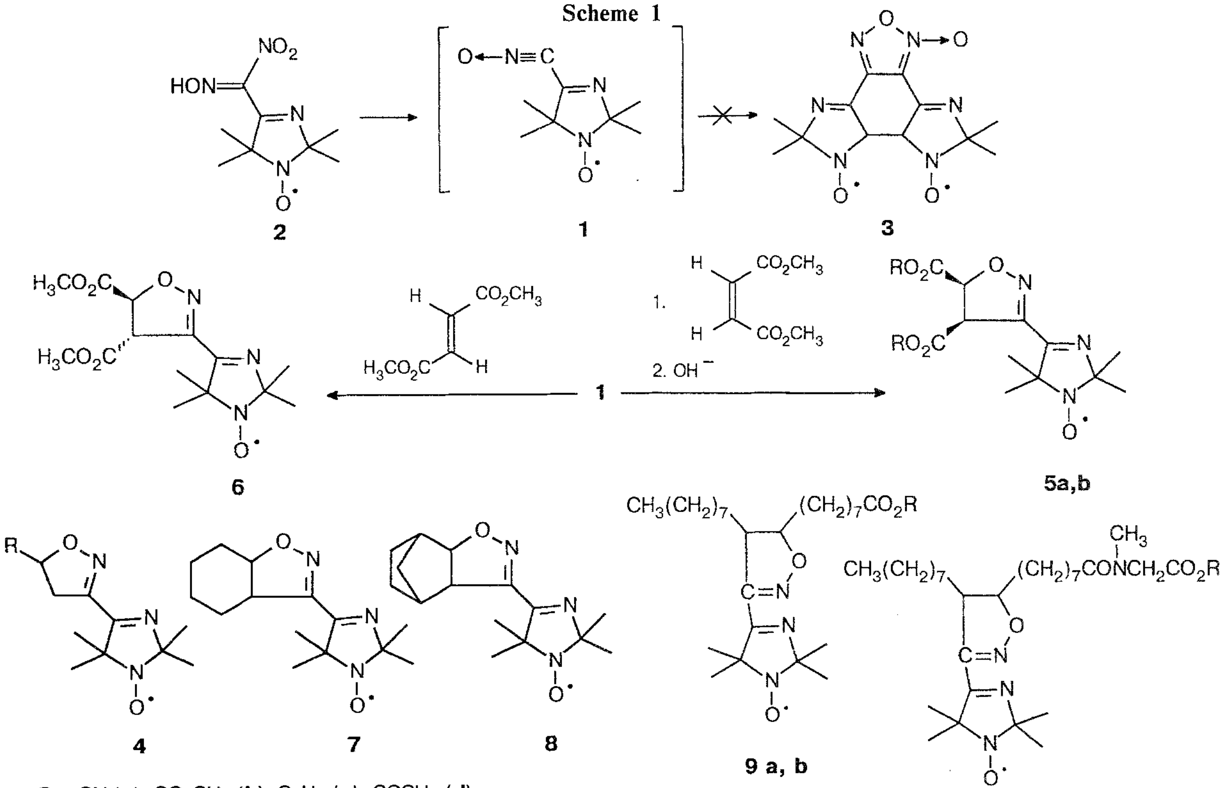
Paramagnetic nitrile oxide, a derivative of 3-imidazoline-1-oxyl, has been generated by thermolysis of geminal nitrooxime. This compound readily undergoes cycloaddition with alkenes with both activated and nonactivated C=C bonds. The paramagnetic nitrile oxide may be used for introducing a nitroxyl into molecules with multiple carbon—carbon bonds.

Key words: nitrile oxide, 3-imidazoline, nitroxyl radical, 1,3-dipolar cycloaddition.

One of the methods for generating nitrile oxides is thermolysis of geminal nitrooximes.[2] Previously we showed that it is applicable to nitrooxime, a diamagnetic derivative of 3-imidazoline 3-oxide.[3] However, the possibility of generating a paramagnetic nitrile oxide derivative of the 3-imidazoline-1-oxyl series (**1**) by the thermolysis of nitrooxime **2** in a similar way (see Ref. 4) seemed questionable, since the nitrous acid evolved in the reaction can cause the loss of the nitroxyl group with the cleavage of the 3-imidazoline ring.[5]

In the present work we showed that the thermal decomposition of nitrooxime **2** occurs at a relatively high rate at 90—100 °C, which makes it possible to use toluene or its mixture with chloroform as the solvent. The loss of the nitroxyl group can be avoided if the reaction is carried out in a nonpolar organic solvent and

Scheme 1



R = CN (**a**), CO$_2$CH$_3$ (**b**), C$_6$H$_5$ (**c**), COCH$_3$ (**d**), (CH$_2$)$_8$CO$_2$CH$_3$ (**e**), (CH$_2$)$_8$CO$_2$H (**f**)

R = CH$_3$ (**a**), H (**b**)

10 a, b

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* For the previous communication, see Ref. 1.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 2, pp. 289—291, February, 1994.

1066-5285/94/4302-0269 $12.50

an inert gas is bubbled through the solution.

One of the characteristic reactions of nitrile oxides is their dimerization to give furoxans.[2] However, thermolysis of nitrooxime **2** affords neither furoxan **3**, nor other paramagnetic products. This cannot be explained by steric hindrance, because a nitrile oxide of a similar structure, a diamagnetic derivative of 3-imidazoline 3-oxide, dimerizes under these conditions to give furoxan.[3] Thermal decomposition of nitrile oxide **1** leads to deep destruction of the imidazoline ring and to the disappearance of the radical site (Scheme 1).

When the thermolysis of nitrooxime **2** is carried out in the presence of an alkene with an activated double bond (acrylonitrile, methyl acrylate, styrene, methyl vinyl ketone), it affords cyclic adducts **4a—d** as a single regioisomer in which substituent R is probably located in position 5 of the isoxasoline ring (*cf.* Refs. 3, 6). Presumably, the cycloaddition occurs stereoselectively, since the reaction of nitrile oxide **1** with dimethyl maleate and dimethyl fumarate gives different cyclic adducts, **5a** and **6**, and hydrolysis of **5a** yields dicarboxylic acid **5b**. The configuration of cyclic adduct **6** depicted in Scheme 1 was chosen on the basis of general considerations of the stereochemistry of 1,3-dipolar cycloaddition.

In the reaction with nonactivated alkenes, cyclohexene and norbornene, nitrile oxide **1** readily forms cyclic adducts (**7** and **8**). Thus, the use of nitrooxime **2** as the precursor of paramagnetic nitrile oxide **1** allows the introduction of a nitroxyl group into a molecule of a substrate containing either activated or nonactivated C=C bonds. Previously, the 1,3-dipolar addition of the paramagnetic aldonitrone derivative of 3-imidazoline 3-oxide was proposed for the introduction of the spin label at the C=C bond.[7] However, the reactivity of nitrones in cycloaddition reactions is much less than that of nitrile oxides. Actually, the cycloaddition of paramagnetic nitrile oxide **1** enables the easy introduction of a spin label at the double bond in molecules of methyl 10-undecenoate, methyl oleate, and *N*-oleylsarcosine; this reaction gives cyclic adducts **4e**, **9a**, and

Table 1. Characteristics of the compounds synthesized

Compound	Yield (%)	M.p.* /°C	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (log ε)	Molecular formula	Found/Calculated (%)		
						C	H	N
4a	75	158—160	1600 (C=N), 2265 (C≡N)	246 (4.15)	$C_{11}H_{15}N_4O_2$	56.4 56.2	6.7 6.4	23.5 23.8
4b	60	Oil	1605 (C=N), 1750 (C=O)	252 (4.30)	$C_{12}H_{18}N_3O_4$	54.0 53.8	6.8 6.7	15.5 15.7
4c	55	127—129	1600 (C=N)	257 (4.18)	$C_{16}H_{20}N_3O_2$	66.9 67.2	7.3 7.0	14.7 14.7
4e	80	Oil	1600, 1625 (C=N), 1740 (C=O)	260 (4.15)	$C_{20}H_{34}N_3O_4$	63.1 63.2	9.0 9.0	11.3 11.1
4f	90	Oil	1600 (C=N), 1710 (C=O)	258 (3.91)	$C_{19}H_{32}N_3O_4$	62.3 62.3	8.6 8.7	11.4 11.5
5a	50	101—103	1585, 1600 (C=N), 1760 (C=O)	250 (4.16)	$C_{14}H_{20}N_3O_6$	51.9 51.6	6.3 6.1	12.7 12.9
5b	90	154—155	1610 (C=N), 1750 (C=O)	252 (4.08)	$C_{12}H_{16}N_3O_6$	48.3 48.3	5.6 5.4	13.9 14.1
6	70	80—81	1590, 1610 (C=N), 1745 (C=O)	250 (4.10)	$C_{14}H_{20}N_3O_6$	51.6 51.6	6.0 6.1	12.8 12.9
7	45	100—102	1560, 1595 (C=N)	262 (4.06)	$C_{14}H_{22}N_3O_2$	63.7 63.7	8.6 8.3	15.5 15.9
8	75	118—120	1575, 1595 (C=N)	260 (4.03)	$C_{15}H_{22}N_3O_2$	65.7 65.3	8.2 8.0	15.2 15.2
9a	70	Oil	1560, 1620 (C=N), 1735 (C=O)	256 (3.80)	$C_{27}H_{48}N_3O_4$	67.5 67.9	9.7 10.0	8.6 8.8
9b	90	Oil	1610 (C=N), 1710 (C=O)	256 (3.92)	$C_{26}H_{46}N_3O_4$	67.2 67.3	9.7 9.9	8.7 9.1
10a	70	Oil	1600 (C=N), 1670, 1760 (C=O)	259 (3.85)	$C_{32}H_{57}N_4O_5$	66.4 66.6	9.9 9.9	9.6 9.7
10b	90	Oil	1620 (C=N), 1670, 1720 (C=O)	260 (3.90)	$C_{31}H_{55}N_4O_4$	66.2 65.9	9.7 9.7	9.6 9.6

* Compounds **4a**, **4c**, and **5a** were purified by recrystallization from a hexane—ethyl acetate mixture; **6** and **7** were recrystallized from hexane; **8** was recrystallized from aqueous ethanol; compounds **4b,e,f**, **9a,b**, and **10a,b** were purified by chromatography on a column with silica gel, $CHCl_3$ was used as the eluent.

10a. Their subsequent hydrolysis smoothly leads to the spin-labeled carboxylic acids **4f**, **9b**, and **10b**, analogs of surfactants. It should be noted that for asymmetrical alkenes, for example, methyl oleate, it is difficult to distinguish the preferential direction of cycloaddition. In this case, a mixture of regioisomers is apparently formed, though this cannot be determined by TLC. For methyl undecenoate, the formation of the 5-substituted isomer seems more likely, taking into account the spatial requirements imposed on the cyclic transition state.

Thus, the generation of paramagnetic nitrile oxide not only opens new possibilities for the synthesis of bi- and polyfunctionally substituted derivatives of nitroxyl radicals, but is probably a versatile method for introducing a nitroxyl-containing moiety into a molecule with multiple carbon—carbon bonds.

Experimental

IR spectra were recorded on a UR-20 spectrometer in KBr pellets (1 mm thick, the concentration was 25 %) and in CCl_4 solutions (the concentration was 5 %). UV spectra were obtained on a Specord UV-VIS spectrophotometer in ethanol. The data from elemental analysis, IR and UV spectra, melting points, and the yields of the compounds synthesized are given in Table 1. Nitrooxime **2** was prepared by the known procedure.[4]

Generation of nitrile oxide 1 and its interaction with alkenes (general procedure). A solution of 10 mmol of nitrooxime **2** in $CaCl_2$-dried $CHCl_3$ was added dropwise to a solution of 20 mmol of alkene in 30 mL of toluene heated to 110 °C; argon was simultaneously bubbled through the solution. After the addition of nitrooxime, a portion of the $CHCl_3$ was evaporated so that the temperature in the boiling mixture increased to 95—100 °C. The mixture was kept at this temperature for 0.5—1 h under argon (TLC monitoring, Silufol UV-254, elution with $CHCl_3$). The solution was concentrated, and cyclic adducts **4—10** were isolated by chromatography on a column with silica gel and $CHCl_3$ as the eluent. The cyclic adduct with methyl vinyl ketone **4d**, m.p. 108—110 °C (*cf.* Ref. 8) was obtained in 60 % yield.

Esters **4e**, **5a**, **9a**, and **10a** were hydrolyzed with a 5 % solution of NaOH in aqueous ethanol (1:1) for 10 h at 20 °C to give the corresponding acids. The solution was concentrated to half its volume, diluted with an equal amount of water, neutralized with 5 % HCl, and extracted with $CHCl_3$. The extract was dried with $MgSO_4$, and the solution was concentrated to give dicarboxylic acid **5b**. Acids **4f**, **9b**, and **10b** were purified by chromatography on a column with silica gel, $CHCl_3$ was used as the eluent.

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Received March 19, 1993