Synthesis and properties of heterocyclic β-nitronitrone: 1,2,2,5,5-pentamethyl-4-nitromethyl-3-imidazoline 3-oxide

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The reaction of methyl nitrone, a derivative of 3-imidazoline 3-oxide, with methyl nitrate in the presence of PhLi results in β-nitronitrone. The tnteraction of the latter with electrophiles involves, as a rule, the methylene group. Nitrile oxide, which is an 3-imidazoline 3-oxide derivative, has been generated by thermolysis of *gem*-nitrooxime. This easily dimerizes to furoxan or undergoes regioselective 1,3-dipolar cycloaddition with alkenes.

Key words: nitrone, β-nitronitrone, 3-imidazoline 3-oxide, nitrile oxide, cycloaddition, nitroxyl radical.

Previously we demonstrated that the reaction of 1-hydroxy-2,2,4,5,5-pentamethyl-3-imidazoline with methyl nitrate in the presence of PhLi results in nitroenamine **1** (*cf.* Ref. 1), which reacts with electrophilic reagents at one or two of the three reaction centers, *viz.*, the enamine C atom, the O atom of the nitro group, or the N atom of the heterocycle,[1—3] and serves as the starting compound for synthesizing various functionally substituted nitroxyl radicals.

It should be noted that nitroenamines are a well studied class of organic compounds, unlike their close analogs, β-nitronitrones. There are almost no data on the reactivity of the latter.

It is known that the treatment of 3-imidazoline 3-oxide (**2**) with PhLi gives a metallated derivative, which readily reacts with esters to give β-oxonitrones.[5] Under similar conditions, the reaction of compound **2** with methyl nitrate in the presence of PhLi results in nitronitrone **3**. In contrast to nitroenamine **1** (*cf.* Ref. 1) and β-oxonitrones of similar structure (*cf.* Ref. 6), compound **3** exists in DMSO and $CDCl_3$ solutions exclusively in the nonconjugated nitronitrone form. Thus, the ^1H NMR spectrum in $CDCl_3$ displays singlets at δ 1.20 (6 H) and 1.40 (6 H) for the 2,5-*gem*-dimethyl groups, at δ 2.32 (3 H) for the N—CH_3 groups, and at 5.17 (2 H) for the CH_2 group. The ^{13}C spectrum contains, *inter alia*, signals for the carbon atom of the nitrone group at δ 135.09 and for the CH_2 group at δ 66.71. The patterns of the spectra do not change on going to a DMSO solution.

In the present work some properties of compound **3** were studied. Nitrone **3** reacts with electrophiles like nitroenamine **1**, although the reaction has some features typical of the β-nitronitrone group. For example, the bromination and nitrosation of **3** occur, as expected, at the methylene carbon atom to give bromo-derivatives **4,5** and nitrooxime **6**, respectively (*cf.* Ref. 1). It should be noted that, according to the ^1H NMR spectral data, the monobromo-derivative **4** also exists in the nonconjugated nitronitrone form. The reaction of compound **3** with formaldehyde in the presence of amines gives alcohol **7**, which readily undergoes dehydration on silica gel to afford nitroolefin **8** (*cf.* Ref. 2).

Previously we showed that the reaction of nitroenamine **1** with acid chlorides results in *O*-acylhydroximoyl chlorides.[3] However, compound **3** reacts with benzoyl chloride under similar conditions to give compound **9**, which is, according to the elemental analysis data, a dibenzoylation product. The IR spectrum of compound **9** displays bands at 1760 and 1780 cm^{-1} (COOR) and at 1590, 1600, and 1610 cm^{-1} (C=C and C=N). The ^1H NMR spectrum of compound **9** contains signals of five methyl groups at δ 1.47 (6 H), 1.50 (6 H), and 2.31 (3 H) and a multiplet for protons of two phenyl groups with a center at δ 7.7. Based on these data, the structure of a dibenzoyl derivative of a hydroximic acid was assigned to compound **9**. The formation of **9** can be represented by a scheme including the initial attack at the O atom of the nitro group, the elimination of $PhCO_2H$ to give nitrile oxide **10** (*cf.* Ref. 3), followed by the addition of $PhCO_2H$ and additional benzoylation.

It is known that the thermolysis of geminal nitrooximes is a mild method for generating derivatives of nitrile oxides.[7] Compound **6** is thermally unstable and readily eliminates an HNO_2 molecule on heating to 80 °C in nonpolar organic solvents to give nitrile oxide **10** (Scheme 2), which under these conditions dimerizes to give furoxan **11** in the absence of substrates containing C=C bonds (*cf.* Ref. 7). It should be noted that the

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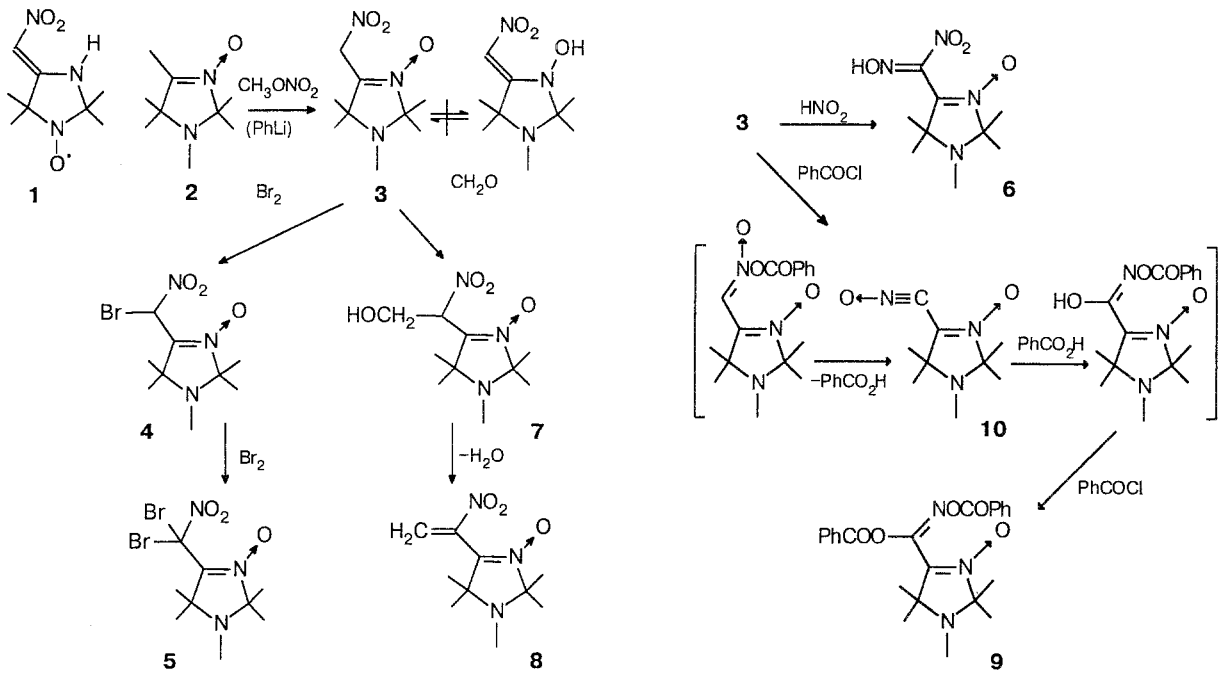
Scheme 1

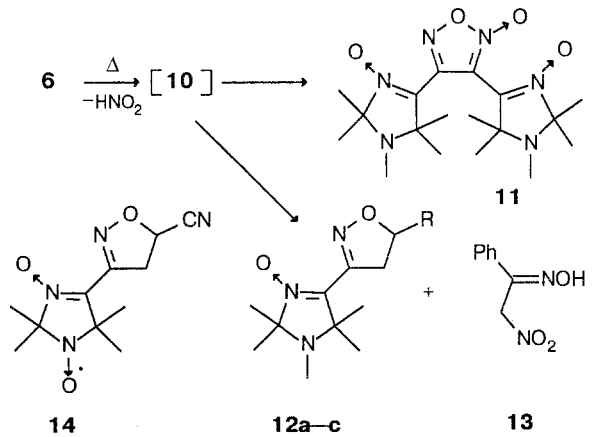


formation of nitrile oxide **10** as an intermediate product of the reaction of the respective geminal chlorooxime with nucleophilic reagents has been postulated previously[8] but has not been unambiguously confirmed.

The thermolysis of nitroxime **6** in the presence of methyl acrylate, acrylonitrile, or styrene results in cycloadducts **12**. In all cases the reaction proceeds regioselectively to give only a 5-substituted isomer (*cf.* Ref. 9). For example, the ^{13}C NMR spectrum of adduct **12a** ($CDCl_3$) contains signals at δ 39.83 (CH_2-4′), 52.49 (CO_2CH_3), 77.65 (CH-5′), 148, and 169.98 (C=N and C=O) along with signals for the carbon atoms of the imidazoline ring. The signals were assigned on the basis of their multiplicity. It is noteworthy that the cycloaddition reaction with styrene results in nitrooxime **13** along with cycloadduct **12c**.

Cycloadduct **12b** readily undergoes oxidation by H_2O_2 in the presence of Na_2WO_4 to give nitroxyl radical **14**. This makes it possible to consider nitroxime **6** as a synthon for introducing a spin label to a substrate molecule containing a C=C bond.

Scheme 2



R = CO_2CH_3 (**a**), CN (**b**), C_6H_5 (**c**)

Experimental

IR spectra were recorded on Specord M-80 and UR-20 spectrophotometers in KBr pellets (concentration 0.25 %) and in solutions (CCl_4 and $CHCl_3$, concentration 5 %). UV spectra were recorded on a Specord UV-VIS spectrometer in ethanol. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC-200 spectrometer in $CDCl_3$ (concentration 5 %). The characteristics of the compounds synthesized are presented in Table 1, and the ^1H NMR spectral data appear in Table 2. Imidazoline **2** was obtained by the known procedure.[10]

1,2,2,5,5-Pentamethyl-4-nitromethyl-3-imidazoline 3-oxide (3). A solution of imidazoline **2** (3.4 g, 20 mmol) in abs. ether (10 mL) was added dropwise with stirring to a solution of phenyllithium prepared from bromobenzene (4.2 mL, 40 mmol) and lithium (0.56 g, 80 mg-at) in abs. ether (50 mL). The mixture was stirred for 20 min at 20 °C, then methyl nitrate (2.5 mL, 40 mmol) was added dropwise with cooling to 0 °C. Stirring was continued for 20 min at 20 °C, water (20 mL) was added, and the ethereal solution was separated. The aqueous solution was washed with ether (3×15 mL) and neutralized with 10 % HCl, and the product was extracted with $CHCl_3$ (3×30 mL). The extract was dried with $MgSO_4$, the solution was concentrated, the residue was washed with

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
3	50	145—147	1600 (C=N), 1360, 1580 (NO_2)	242 (4.03)	$C_9H_{17}N_3O_3$	50.5 / 50.5	8.1 / 7.9	19.5 / 19.5
4	65	136—137	1600 (C=N), 1345, 1580 (NO_2)	258 (3.95)	$C_9H_{16}BrN_3O_3$**	36.8 / 36.7	5.5 / 5.4	14.1 / 14.3
5	70	108—110	1590 (C=N), 1350, 1565 (NO_2)	270 (3.75)	$C_9H_{15}Br_2N_3O_3$**	29.1 / 29.0	4.1 / 4.0	11.1 / 11.3
6	100	103—104	1645, 1595 (C=N), 1325, 1545 (NO_2)	238 (4.06) 342 (4.02)	$C_9H_{16}N_4O_4$	42.2 / 42.7	6.2 / 5.9	21.9 / 22.1
7	30	173—175	1605 (C=N), 1370, 1570 (NO_2)	235 (3.90)	$C_{10}H_{19}N_3O_4$	48.8 / 49.0	7.5 / 7.7	17.3 / 17.2
8	10	119—121	1605 (C=N), 1375, 1570 (NO_2)	233 (3.81) 360 (3.97)	$C_{10}H_{17}N_3O_3$	52.5 / 52.9	7.7 / 7.5	18.2 / 18.5
9	60	114—115	1780, 1760 (C=O), 1610, 1585 (C=N)	227 (4.36) 384 (3.82)	$C_{23}H_{25}N_3O_5$	65.2 / 65.2	5.9 / 5.9	10.0 / 10.0
11	75	208—209	1550, 1590 (C=N)	243 (3.92) 287 (4.00)	$C_{18}H_{30}N_6O_4$	54.7 / 54.8	7.6 / 7.6	21.1 / 21.3
12a	50	98—99	1740 (C=O) 1520, 1550 (C=N)	294 (4.14)	$C_{13}H_{21}N_3O_4$	55.2 / 55.1	7.7 / 7.4	14.5 / 14.8
12b	50	114—116	2245 (C=N), 1540, 1555 (C=N)	295 (4.16)	$C_{12}H_{18}N_4O_2$	57.2 / 57.6	7.0 / 7.2	22.4 / 22.4
12c	60	115—116	1560 (C=N)	292 (4.13)	$C_{17}H_{23}N_3O_2$	67.8 / 67.8	7.7 / 7.6	13.9 / 14.0
14	60	179—181	2250 (C=N), 1525, 1555 (C=N)	—	$C_{11}H_{15}N_3O_3$	55.8 / 55.7	6.4 / 6.4	17.6 / 17.8

* Compounds **3**—**5** were purified by recrystallization from a hexane—ethyl acetate mixture. Compounds **7**—**14** were purified by recrystallization from hexane. Compound **6** had the correct elemental analysis data without purification. ** Br, Found/Calculated (%): 26.8/27.2 (**4**), 42.4/42.9 (**5**).

hexane, and the precipitate of compound **3** was filtered off. ^{13}C NMR ($CDCl_3$), δ: 23.41, 23.63 (2,5-$(CH_3)_2$); 26.65 (N—CH_3); 62.60 (C-5); 66.71 (—CH_2NO_2); 90.51 (C-2); 135.09 (C-4). ^{13}C NMR (DMSO-d_6), δ: 23.07, 23.52 (2,5-$(CH_3)_2$); 26.69 (N—CH_3); 62.57 (C-5); 67.60 (—CH_2NO_2); 89.70 (C-2); 135.63 (C-4).

Table 2. ^1H NMR spectral data for the compounds synthesized

Compound	δ ($CDCl_3$), J/Hz N—CH_3	2-CH_3	5-CH_3	4-R
3	2.32	1.40	1.20	5.17 (2 H)
4	2.36	1.30 1.43	1.42	6.74 (1 H)
9	2.31	1.50	1.47	7.7 (m, 1 OH, Ph)
12a	2.35	1.42	1.42	3.75 (s, 3 H, OCH_3); 3.9 (m, 2 H, —CH_2—), 5.04 (m, 1 H, CH)
12b	2.37	1.42 1.44	1.43 1.49	ABX-system, 4.01 (J_{AB} = 19, J_{AX} = J_{BX} = 6, 2 H, AB, 5.24 (dd, J_{AX} = 6, 1 H)
12s	2.37	1.44 1.47	1.46 1.49	3.66 (dd , J_{AB} = 18, J_{AX} = 9, 1 H), 4.08 (dd, J_{AB} = 18, J_{BX} = 9, 1 H) 5.63 (t, J = 9, 1 H, 7.32 (br.s, 5 H, C_6H_5)

4-Bromonitromethyl-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide (4). A solution of bromine (0.1 mL, 2 mmol) in methanol (5 mL) was added dropwise with stirring to a solution of nitronitrone **3** (0.43 g, 2 mmol) in 10 mL of a methanolic solution of sodium methoxide prepared from sodium (0.05 g, 2 mg-at) and methanol (10 mL). The solution was concentrated, the residue was washed with water, and the precipitate of compound **4** was filtered off and dried. An additional amount of compound **4** was obtained by extracting the aqueous solution with $CHCl_3$.

When the amounts of sodium methoxide and bromine were doubled, dibromo-derivative **5** was obtained under similar conditions.

4-Hydroxyiminonitromethyl-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide (6). Aqueous HCl (5 %, 25 mL) was added dropwise with cooling to 0 °C and stirring to a solution of nitronitrone **3** (0.43 g, 2 mmol) and $NaNO_2$ (0.17 g, 2.5 mmol) in 10 % aqueous NaOH (10 mL). Stirring was continued for 30 min at 20 °C, and the precipitate of nitroxime **6** was filtered off, washed with water, and dried.

4-(2-Hydroxy-1-nitroethyl)-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide (7) and 1,2,2,5,5-pentamethyl-4-(1-nitrovinyl)-3-imidazoline 3-oxide (8). A solution of nitronitrone **3** (0.43 g, 2 mmol), 30 % formaldehyde (1 mL), and diethylamine (0.65 mL, 6.3 mmol) in methanol (10 mL) was

kept for 30 min at 20 °C, concentrated, and diluted with water (10 mL). The products were extracted with $CHCl_3$, the extract was dried with $MgSO_4$, and the solution was concentrated. Compounds **7** and **8** were separated by chromatography on a column with silica gel using $CHCl_3$ as the eluent. Compound **8** was eluted first.

***O,O'*-Dibenzoyl-1,2,2,5,5-pentamethyl-3-imidazoline-4-carbohydroximic acid 3-oxide (9).** A solution of benzoyl chloride (0.86 mL, 7.5 mmol) in $CHCl_3$ (5 mL) was added dropwise with cooling to 0 °C and stirring to a solution of nitronitrone **3** (0.65 g, 3 mmol) and triethylamine (1.04 mL, 7.5 mmol) in $CHCl_3$ (30 mL). The solution was concentrated, the residue was washed with dry ether (5×20 mL), and the precipitated salts were filtered off. The solution was concentrated, the residue was washed with hexane, and the precipitate of compound **9** was filtered off.

3,4-Bis(1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide-4-yl)-1,2,5-oxadiazole 2-oxide (11). A suspension of nitrooxime **6** (0.49 g, 2 mmol) in benzene (50 mL) was heated to 80 °C over 30 min while a flow of argon passed through the solution. The mixture was kept for 10 min at this temperature, and the solution was concentrated. Compound **11** was isolated by chromatography on a column with silica gel using $CHCl_3$ as the eluent.

Under similar conditions, thermolysis in the presence of methyl acrylate, acrylonitrile, or styrene (5 mmol) gives **4-(5-R-2-isoxazolin-3-yl)-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxides (12a—c).** ^{13}C NMR spectrum for cycloadduct **12a** ($CDCl_3$), δ: 23.95, 24.13 (2,5-$(CH_3)_2$); 26.59 (N—CH_3); 39.89 (—CH_2—); 52.49 (—CO_2CH_3); 63.75 (C-5); 77.65 (CH—CO_2—); 91.11 (C-2); 136.60 (C-4); 148.46 (C-3′); 169.98 (C=O). ^{13}C NMR spectrum of compound **12c** ($CDCl_3$), δ: 23.99, 24.08, 24.12 (2,5-$(CH_3)_2$); 26.63 (N—CH_3); 43.31 (—CH_2—); 63.78 (C-5); 82.71 (—CH—O); 90.86 (C-2); 125.68, 128.03, 128.50, 140.09 (C_6H_5); 137.33 (C-4); 148.86 (C-3′).

4-(5-Cyano-4,5-dihydroisoxazol-3-yl)-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxide (14). A solution of nitrile **12b** (0.13 g), 30 % H_2O_2 (0.5 mL), and a catalytic amount of Na_2WO_4 and trilon B in a mixture of methanol (3 mL) and acetonitrile (3 mL) was kept for 15 min at 70 °C. The solution was diluted with water (20 mL), and the product was extracted with $CHCl_3$ (5×10 mL). The extract was dried with $MgSO_4$ and concentrated. Compound **14** was isolated by chromatography on a Silufol-UV 254 plate (20×20 cm) using $CHCl_3$ as the eluent.

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