Tetrahedron 66 (2010) 3608–3613

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

2-Substituted nitrones and isomeric hydroxylamines – obtained via aluminium amalgam reduction of nitro nitriles and ketones—a new access to convenient intermediates for nitroso carbonyl compounds preparation

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ARTICLE INFO

Article history:
Received 30 November 2009
Received in revised form 16 February 2010
Accepted 8 March 2010
Available online 17 March 2010

Keywords:
Nitro nitriles
Hydroxylamines
Cyclic nitrones
Aluminium amalgam reduction
Nitroso nitriles

ABSTRACT

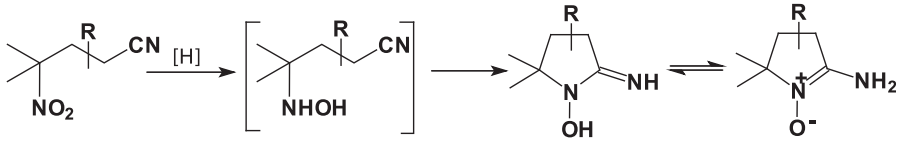
Substituted five-membered cyclic nitrones (pyrroline *N*-oxides) have been obtained in good to high yields from tertiary γ-nitro ketones and nitriles employing aluminium amalgam as a reducing agent in moist diethyl ether or THF. Attempts to obtain cyclic amino nitrones from α- or β-nitro nitriles failed and only the corresponding hydroxylamines have been isolated. Both nitrones and hydroxylamines have been used for synthesis of tertiary *C*-nitroso nitriles or ketones.

1. Introduction

Five-membered cyclic nitrones (pyrroline *N*-oxides) have been widely used in organic syntheses[1] as well as in free radical studies employing an Electron Paramagnetic Resonance (EPR) technique.[2] 3,4-Dihydro-2,2-dimethyl-2*H*-pyrrole-1-oxide (or 5,5-dimethyl-1-pyrroline-1-oxide, DMPO) and its derivatives were originally introduced in 1973 by Janzen;[3] these compounds have been largely applied as radical scavengers.[2] Over the past few years some DMPO derivatives with a 2-alkyl or 2-aryl substituent have acquired importance.[4] 5,5-Dialkyl-2-alkylpyrroline-1-oxides may be as well convenient intermediates for the preparation of tertiary γ-nitroso carbonyl compounds.[5]

2-Alkyl derivatives of DMPO have been obtained by reduction of the appropriate γ-nitro ketones using usually Zn dust,[6] in most cases with aq ammonium chloride.[4a,7] Catalytical (Pd on charcoal) hydrogenation in methanol has also been successfully applied.[8]

2-Amino derivatives of DMPO have been also employed as model compounds in EPR studies on biological systems.[9] 2-Amino nitrones have usually been obtained by reduction of the appropriate γ-nitro nitriles (Scheme 1).[10] However, the most often used systems such as Fe/HCl,[10] Zn/NH_4Cl aq,[5,10] Zn/AcOH,[11] or catalytical hydrogenation[10] are not convenient due to the long reduction time, zinc activation requirement, and the troublesome isolation of highly polar and hygroscopic products from the aqueous or alcoholic reaction mass. Buckley and co-workers[10] suggested that an intermediate hydroxylamine was the primary reduction product and the cyclization to the appropriate amino nitrone subsequently occurred via its tautomeric form. Attempts to isolate the intermediate hydroxylamine failed[10] (Scheme 1).



Scheme 1. General method to obtain the cyclic amino nitrone from a nitro nitrile.[10]

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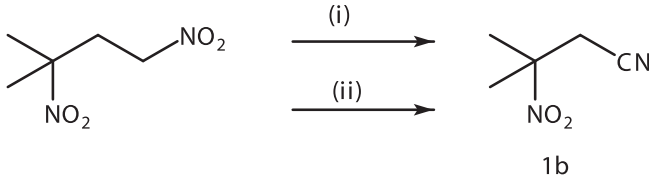
doi:10.1016/j.tet.2010.03.023

During our research, some unstable aliphatic tertiary *C*-nitroso nitriles and ketones had to be obtained for the purpose of some mass spectrometric (MS) and ^{14}N NMR studies.[12] Since the direct reduction of aliphatic nitro compounds to corresponding nitroso compounds usually does not occur,[13] we needed a quick and efficient method for reduction of the tertiary α-, β- and γ-nitro carbonyl compounds to intermediates, e.g., hydroxylamines or nitrones, and then oxidation to the appropriate *C*-nitroso compounds. In this paper, such a method is described and discussed.

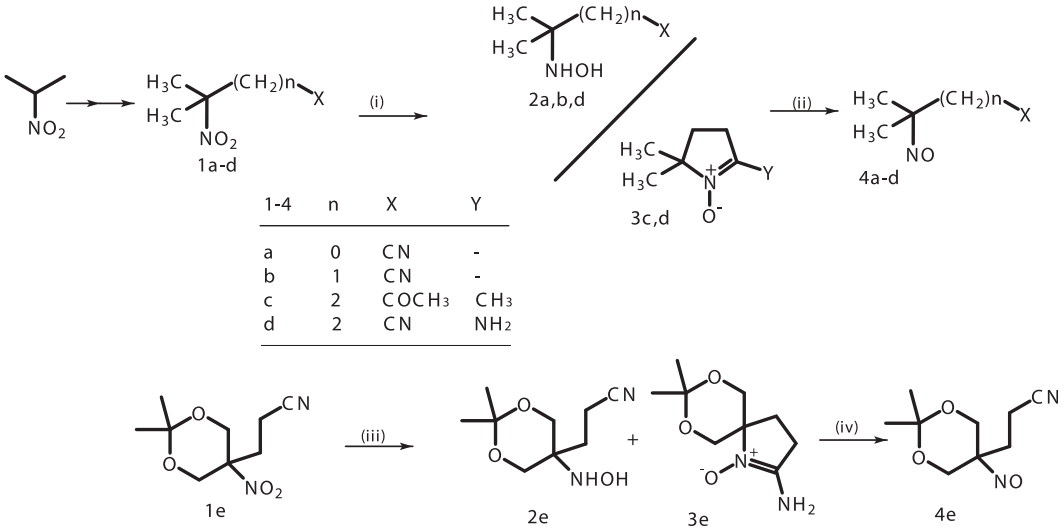
2. Results and discussion

The nitro compounds **1** were reduced with aluminium amalgam to afford corresponding hydroxylamines **2** and/or nitrones **3** (the latter in the case of the γ-nitro compounds). **2** and/or **3** were oxidized to the nitroso compounds **4** (Scheme 2).

amounts of the appropriate aldehyde and some other decomposition products. Instead of this, we used a modified phosphorus trichloride reduction method[21] in dry pyridine at rt, and 3-methyl-3-nitrobutanenitrile (**1b**) was smoothly obtained in 81% yield (Scheme 3).



Scheme 3. Reduction of 3-methyl-1,3-dinitrobutane to 3-methyl-3-nitrobutanenitrile (**1b**), (i): $NaBH_2S_3$/THF, reflux, 5 h, 62%, (ii): PCl_3/pyridine, rt, two days, 81%.



Scheme 2. Synthesis of the target nitroso compounds **4** from the corresponding nitro compounds **1**; (i): Al/Hg, Et_2O/H_2O, rt, 18–85%; (ii): Cl_2/H_2O, 0 °C or MCPBA/$CHCl_3$, 0 °C or $NaIO_4/H_2O$, rt, 21–92%, (iii): Al/Hg, THF/H_2O, rt, 92%, (iv): $NaIO_4/H_2O$, rt, 77%.

2.1. Syntheses of starting nitro compounds

2-Methyl-2-nitropropanenitrile (**1a**) was obtained by oxidative substitution of 2-nitropropane sodium salt in water with sodium cyanide/potassium ferricyanide in 67% yield according to Ref. 14.

5-Methyl-5-nitrohexan-2-one (**1c**) and 4-methyl-4-nitropentanenitrile (**1d**) were synthesized via Michael addition of 2-nitropropane to methyl vinyl ketone[15] or acrylonitrile,[16] respectively, using catalytic amounts of 40% aq tetrabutyl ammonium hydroxide (TBA).

5-(2-Cyanoethyl)-2,2-dimethyl-5-nitro-1,3-dioxane (**1e**) was obtained in a four step synthesis starting from aldolization of nitromethane and formaldehyde, then cyclization of the resulting nitro triol with acetone followed by dehydrometylation and eventually Michael addition to acrylonitrile.[17,18]

To the best of our knowledge, the synthesis of 3-methyl-3-nitrobutanenitrile (**1b**) has not been described in the literature. In order to successfully synthesise the compound, the following reaction pattern was developed. Acetylation of 2-nitroethanol followed by elimination of acetic acid gave not isolated nitroethene, which was subsequently condensed with 2-nitropropane to afford 3-methyl-1,3-dinitrobutane according to Troitskaya.[19] Attempts at the selective reduction of CH_2NO_2 group to nitrile in 3-methyl-1,3-dinitrobutane with $NaBH_2S_3$ in tetrahydrofuran (Lalancette method[20]) gave the nitro nitrile **1b** in 62% yield with considerable

2.2. Reduction of nitro compounds

We used the aluminium amalgam to reduce the nitro derivatives **1**. In our hands, the precipitated aluminium oxide was filtered off after the reduction, and the practically pure nitrone and/or hydroxylamine were obtained after removing the solvent from the filtrate. This technique avoids the inconvenient product isolation from an aqueous solution after the reaction.

Tertiary γ-nitro ketones with the keto group protected as a dimethyl ketal were reduced with aluminium amalgam in moist diethyl ether[22] affording the corresponding hydroxylamines.[23] In this paper, the modified reduction procedure with aluminium amalgam was applied to an unprotected γ-nitro ketone as well as a series of α-, β- and γ-nitro nitriles. The appropriate hydroxylamines and/or nitrones were synthesized in mostly good to high yields. The results obtained for the reduction of **1a**–**e** are presented in Table 1.

The aluminium amalgam reduction of the α-nitro nitrile **1a** afforded significant amounts of decomposition products and 2-hydroxylamino-2-methylpropanenitrile (**2a**) was only isolated in poor yield (18%) (Table 1). Among the decomposition products we searched for the hypothetical cyclic three-membered amino nitrone (unknown to date) but no evidence for such compounds were noticed. The same hydroxylamine **2a** was obtained by the direct addition of hydrocyanic acid to acetone oxime[24] in slightly better yield (27%).

Table 1
Preparation of hydroxylamines **2** and nitrones **3** by the reduction of nitro ketones and nitriles **1** using aluminium amalgam

1	Starting material (nitro group position)	X	Y	Isolated product **2** and/or **3**	Reaction time, h	Yield [%]
a	(α)	CN	n/a	**2a**	0.75	18
b	(β)	CN	n/a	**2b**	1	74
c	(γ)	$C(O)CH_3$	CH_3	**3c**	0.5	88
d	(γ)	CN	NH_2	**2d**→**3d**	0.75	85
e	(γ)	CN	NH_2	**2e**+**3e** (7:3)	2	92

The aluminium amalgam reduction was checked for a β-nitro nitrile as well. 3-Methyl-3-nitrobutanenitrile **1b** was smoothly reduced, but as distinct of the γ-nitro nitriles, only the corresponding hydroxylamine, 3-hydroxylamino-3-methylbutanenitrile (**2b**) was isolated in 74% yield. No cyclization of compound **2b** affording the cyclic 2-amino nitrone has been observed, although a limited number of four-membered cyclic nitrones have been described in the literature.[1d]

The Al(Hg) reduction of 5-methyl-5-nitrohexan-2-one (**1c**) afforded directly a nitrone—3,4-dihydro-2,2,5-trimethyl-2*H*-pyrrole 1-oxide (**3c**). No intermediate hydroxylamine **2c** has been isolated.

The reduction of 4-methyl-4-nitropentanenitrile (**1d**) afforded a viscous, colourless, slowly solidifying oil. The comparison of the properties of the obtained colourless crystals with the literature data showed that the solid was practically pure 2,3-dihydro-2,2-dimethyl-4*H*-pyrrol-5-ylamine 1-oxide (or 2-amino-5,5-dimethyl-1-pyrroline 1-oxide) (**3d**). The following assumption has been made: the first reduction product was the oily hydroxylamine **2d**, which subsequently slowly cyclized affording the crystalline nitrone **3d**. Actually, since in some cases the oil obtained after reduction did not solidify rapidly we could record its IR spectrum. As distinct from the solid product, only weak bands characteristic of amino nitrone:[25] C=N at 1686 cm^{-1} and N–O at 1200 cm^{-1} were found, whereas a strong C≡N group band at 2243 cm^{-1} was observed in the spectrum. Only after solidification did the obtained crystals give the IR, ^1H NMR, and mass spectra completely consistent with the nitrone literature data.[25–27] This observation fully confirmed the above assumption that the direct aluminium amalgam reduction product was hydroxylamine **2d**, which subsequently cyclized into amino nitrone **3d**.

After Al(Hg) reduction of 5-(2-cyanoethyl)-2,2-dimethyl-5-nitro-1,3-dioxane (**1e**), an equilibrium mixture containing both the hydroxylamine **2e** and the spirocyclic nitrone **3e** in the ratio of ca. 7:3 (^1H NMR) was obtained. As distinct from the compound **2d**, the hydroxylamine **2e** was very stable and did not fully cyclize even after four months and several crystallization attempts. Only reflux of crude reduction product in the presence of tetramethylguanidine (TMG) for 5 h afforded pure spirocyclic nitrone – 8,8-dimethyl-1-oxy-7,9-dioxa-1-azaspiro[4.5]dec-1-en-2-ylamine (**3e**). On the analogy of 5-hydroxy-1,3-dioxane derivatives,[28] the high stability of the hydroxylamine **2e** can be explained by a bifurcated intramolecular hydrogen bond formation between NHO–H group and oxygen atoms in the dioxolane ring (Scheme 4).

The possibility of the hydrogen bond existence was confirmed in the ^1H NMR spectra carried out in different solvents. Thus, the signals in the hydroxylamine **2e** spectrum were strongly shifted after changing the solvent from $CDCl_3$ chloroform into protic CD_3OD whereas the chemical shifts in the spectrum of nitrone **3e** did not practically depend on the applied solvent.

2.3. Oxidation of hydroxylamines and nitrones to nitroso compounds

All hydroxylamines **2a**, **b**, **d**, **e**, and nitrones **3c**–**e** were subsequently smoothly oxidized:

- into the α-nitroso nitrile **4a** using chlorine in iced water[29,30] in 92% yield,[12a]
- into β- and γ-nitroso nitriles **4b**, **4d**, **4e** using sodium iodate in water[5] in 21-77% yield,
- into the corresponding γ-nitroso ketone **4c** using *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform[31] in 66% yield, appropriately.

All nitroso compounds **4a**–**e** were isolated as crystalline uncoloured dimers (Table 2):

Table 2
Preparation of nitroso compounds **4** by oxidation of nitrones or hydroxylamines

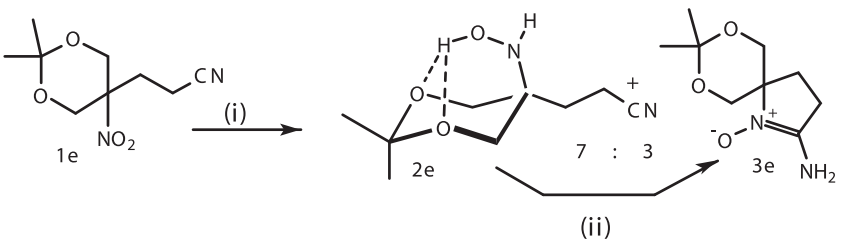
Starting material **2** and/or **3**	Oxidation conditions	Isolated Product, **4**	Reaction time, min	Yield [%]
2a	Cl_2/H_2O, 0 °C	**4a**	5	92
2b	$NaIO_4$, H_2O, rt	**4b**	30	21
3c	*m*-CPBA, $CHCl_3$, 0 °C	**4c**	120	66
2d, **3d**	$NaIO_4$, H_2O, rt	**4d**	30	35
2e, **3e**	$NaIO_4$, H_2O, rt	**4e**	30	77

$$2R'-N=O \rightleftarrows R'-(O\leftarrow)N=N(\rightarrow O)-R'$$

In solution, after melting and even in the gas phase[12a] the dimers are in equilibrium with deep blue monomers R′-N=O. All dimers showed in the IR spectra the characteristic (O←)N=N(→O) band at 1216–1296 cm^{-1}. In the MS of the aliphatic tertiary *C*-nitroso carbonyl compounds and nitriles, there have been observed neither dimer $2M^{+\bullet}$ nor monomer $M^{+\bullet}$ molecular ions, but only the specific MH^+ ions were found. The MH^+ ions intensities were not strongly concentration dependent, so they were not chemical auto-ionization products, but rather ions that were formed in the fragmentation patterns of the absent from the EI mass spectra dimer molecular ions $2M^{+\bullet}$.[12a]

3. Conclusions

The modified aluminium amalgam reduction of γ-nitro ketones and nitriles was checked as an alternative method for the corresponding five-membered nitrones (2-substituted DMPO



Scheme 4. Reduction of 5-(2-cyanoethyl)-2,2-dimethyl-5-nitro-1,3-dioxane (**1e**) affording hydroxylamine **2e** and nitrone **3e** (7:3 mol/mol), (i): Al(Hg), THF/H_2O, rt, 2 h, 92%; (ii): TMG/THF, reflux, 5 h.

derivatives) preparation. The reduction of the lower homologues, β- and α-nitro nitriles, afforded only corresponding hydroxylamines, and no cyclic nitrone formation has been observed. Nitrones and hydroxylamines were easily transformed into corresponding tertiary *C*-nitroso ketones or nitroso nitriles.

4. Experimental

4.1. General

^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini-200 spectrometer at 200 MHz in $CDCl_3$, unless otherwise stated. Chemical shifts values are given in δ [ppm] units relative to TMS. ^{14}N NMR spectra were measured with a Bruker AM500 spectrometer at 36.14 MHz in acetone at 35 °C, nitrogen chemical shifts values were measured in δ [ppm] units using nitromethane as an internal standard. The Fourier-transform infrared (FTIR) spectra were recorded on a Perkin-Elmer FTIR 1640 spectrophotometer; ν_{max} in cm^{-1}. The electron ionization mass spectra (EIMS) at 70 eV and fast ion bombardment (Cs^+) mass spectra (FIB-MS) were recorded on an AMD-604 mass spectrometer.

Unless otherwise stated, commercial grade chemicals were used without further purification. Commercial aluminium foil, thickness 13 μm was used. Flash chromatography and chromatographic filtration were performed using a 230–400 mesh silica gel (Merck). The solvents were purified and/or distilled before use and stored under dry argon, when necessary.

The known nitro compounds **1a**,[14] **1c**,[15] **1d**[10] and **1e**[18] were prepared according to the literature.

*4.1.1. 3-Methyl-3-nitrobutanenitrile (**1b**).* Phosphorus trichloride (6.3 g, 4 mL, 45.8 mmol) was slowly added with stirring at rt to a solution of 3-methyl-1,3-nitrobutane[19] (3.141 g, 19.4 mmol) in dry pyridine (20 mL) under argon. The red-brown reaction mixture was stirred under argon for two days at rt, then cooled to 0 °C and diluted hydrochloric acid (3 mol/L, 120 mL) was carefully added. The reaction mixture was washed with ethyl ether (20 mL×5). The combined separated organic layers were washed with diluted hydrochloric acid (3 mol/L, 20 mL×2) and dried over magnesium sulfate. The solution was concentrated under vacuum, affording a yellow oil that solidized at rt. After vacuum distillation (60 °C/0.3 Torr), a colourless, viscous, solidifying oil of the β-nitro nitrile **1b** (2.015 g, 15.7 mol) was obtained in 81% yield. Mp. 65–68.5 °C (white solid, petroleum ether); FTIR (film): 2975 (C–H), 2252 (C≡N), 1545 (NO_2), 856 (C–N); ^{1}H NMR: 1.72 (s, 6H, $2CH_3$), 2.92 (s, 2H, CH_2); ^{14}N NMR:[12b] −17.47 (NO_2), 126.54 (CN); MS, *m*/*z* (int.%):[32] 82 (100, $[M-NO_2]^+$), 81 (5, $[M-HNO_2]^{+\bullet}$), 55 (93, $C_4H_7^+$), 41 (49); elemental analysis: found C 47.05, H 6.50, N 21.98, calculated for $C_5H_8N_2O_2$, C 46.87, H 6.29, N 21.86%.

*4.1.2. 3-Methyl-3-nitrobutanenitrile (**1b**).* Compound **1b** via the Lalancette reduction (according to[20] with some modifications). To a mixture of sodium borohydride (0.756 g, 0.02 mol) and sulfur (1.92 g, 0.06 mol), 15 mL of dry tetrahydrofuran was rapidly added without cooling and with stirring. 3-Methyl-1,3-dinitrobutane[19] (3.24 g, 0.02 mol) in 5 mL of THF was added dropwise to the obtained resulting suspension of 0.02 mol of $NaBH_2S_3$. The reaction mixture was heated to reflux for 5 h. The temperature was then allowed to cool to rt and the reaction mixture was hydrolyzed by addition of 10% aq hydrochloric acid (10 mL) and stirring overnight at rt. The product was extracted with methylene chloride and the organic phase was washed twice with water (10 mL×2), dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure using a rotary evaporator, affording the oily product (2.43 g). FTIR (film): 2250 (C≡N), 1700 (C=O), 1545 (NO_2). According to the GC–MS analysis, the product was a mixture of 3-methyl-3-nitrobutanenitrile (**1b**) (62%), 3-methyl-3-nitrobutyraldehyde (27%), 2-methyl-4-nitrobut-2-ene (6%), senecioaldehyde ($(CH_3)_2C$=CH–CHO (2%) and some minor components.

4.2. General procedure for reduction of nitro compounds 1a–e with aluminium amalgam

4.2.1. Aluminium amalgam (modified procedure[22]). Commercial aluminium foil (0.255 g, 9.58 mmol) was cut into ca. 20 strips, and each strip was rolled into a cylinder about 5 mm in diameter using a glass tube. Each of the aluminium foil cylinders was degreased by immersing it in ethyl ether, dried in air for several seconds, and amalgamated by immersing one by one for 15 s in a solution of mercury (II) chloride (0.07 g) in water (4 mL). Each amalgamed cylinder was then quickly transferred into a three neck flask containing diethyl ether (15 mL) and water (0.13 mL). The reaction mixture was stirred vigorously for 30 min at rt before the reduction was carried out.

4.2.2. Aluminium amalgam reduction. A solution of the appropriate nitro compound **1a**–**e** (5 mmol) in diethyl ether or tetrahydrofuran (5 mL) was added dropwise to a flask containing Al(Hg) at such a rate that the solvent refluxed briskly. The reaction mixture was stirred for 0.5–7 h at rt until all the starting material was consumed. The cellulose powder (Whatman, 0.1 g) was subsequently added into resulted white-grey suspension and the reaction mixture was filtered through a cellulose bed. The alumina precipitate was washed in the case of nitro ketones with ethyl ether (5 mL×5), and in the case of nitro nitriles subsequently with ethyl ether (5 mL×2), dichloromethane (5 mL×2) and dichloromethane/methanol 1:1 (v/v) (5 mL×3). The solvent was removed under vacuum, and the obtained crude products were purified by distillation (**2c**) or crystallization (**2a**, **2d**,**e**) (Table 1).

*4.2.3. 2-Hydroxylamino-2-methylpropanenitrile (**2a**) (starting from compound **1a**[14] according to the general procedure).* A solution of 2-methyl-2-nitropropanenitrile (**1a**, 570 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminium foil and mercury (II) chloride, following the general procedure. The crystallization of the crude product (33% pentane/Et_2O) gave the *title compound* **2a** (90 mg, 18%) as a white solid, mp 90–92 °C (lit.[24] 98–99 °C). FTIR (KBr pellet): 3260 (O–H, N–H), 2990 (C–H), 2240 (C≡N), 1065 (N–O); MS, *m*/*z* (int.%): 100 (30, $M^{+\bullet}$), 84 (23, $[M-CN]^+$), 69 (61), 57 (100).

*4.2.4. 3-Hydroxylamino-3-methylbutanenitrile (**2b**) (starting from compound **1b** according to the general procedure).* A solution of 3-methyl-3-nitrobutanenitrile (**1b**, 640 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminium foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2b** 422 mg (74%), a bluish oil, directly oxidized to the corresponding β-nitroso nitrile **4b**. FTIR (film): 3259 (O–H, N–H), 2978 (C–H), 2250 (C≡N); ^{1}H NMR: 1.25 (s, 6H, $2CH_3$), 2.60 (s, 2H, CH_2); MS, *m*/*z* (int.%): 114 (0.2, $M^{+\bullet}$), 99 (5, $[M-CH_3]^+$), 82 (18), 74 (100), 56 (35).

*4.2.5. 2,2,5-Trimethyl-1-oxy-3,4-dihydro-2H-pyrrole (**3c**) (starting from compound **1c**[15] according to the general procedure).* A solution of 5-methyl-5-nitrohexan-2-one (**1c**, 795 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminium foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2c** 559 mg (88%). A colourless oil, bp 48–50 °C/1 Torr (lit.[33]

71–72 °C/2 Torr). FTIR (film): 2971 (C–H), 1605 (C═N), 1236 (N–O); ^{1}H NMR: 1.40 (s, 6H, $2CH_3$), 2.00 (t, 2H, J 7.5 Hz, C–CH_2CH_2), 2.03 (s, 3H, $COCH_3$), 2.59 (t, 2H, *J* 7.5 Hz, C-CH_2CH_2); MS, *m*/*z* (int.%): 127 (78, $M^{+\bullet}$), 112 (35, $[M-CH_3]^+$), 95 (25), 69 (23), 55 (46), 41 (100).

*4.2.6. 5,5-Dimethyl-1-oxy-4,5-dihydro-3H-pyrrol-2-ylamine (**3d**) (starting from compound **1d**[10] according to the general procedure).* A solution of 4-methyl-4-nitropentanenitrile (**1d**, 710 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminium foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **3d** 544 mg (85%). A colourless, viscous oil of **2d** solidified into white crystals of **3d**. Mp 218–220 °C (dec), white plates, lit.[10] 238 °C (dec). FTIR (KBr pellet): 3200 (N–H), 2970 (C–H), 1690 (C═N), 1200 (N–O); ^{1}H NMR (CD_3OD): 1.31 (s, 6H, $2CH_3$), 1.98 (t, 2H, *J* 7.5 Hz, C–CH_2CH_2), 2.65 (t. 2H, *J* 7.5 Hz, C–CH_2CH_2); MS, *m*/*z* (int.%): 128 (100, $M^{+\bullet}$), 113 (43, $[M-CH_3]^+$), 111 (24), 96 (58), 82 (9), 69 (20).

*4.2.7. 5-(2-Cyanoethyl)-2,2-dimethyl-5-hydroxylamine-1,3-dioxane (**2e**) and 2-amino-8,8-dimethyl-1-oxy-1-aza-7,9-dioxaspiro[4.5]dec-2-ene (**3e**).* A solution of the nitrile **1e** (0.783 g, 3.66 mmol) in tetrahydrofuran/ether (15 mL, 2:1 v/v) was added to Al(Hg) prepared from aluminium foil (0.187 g, 7 mmol) and mercury (II) chloride (0.05 g) in THF (11 mL) containing water (0.1 mL) according to the general procedure. A colourless solid, mp 170–174 °C dec, (33% chloroform/hexane), containing the hydroxylamine **2e** (70%) and the spirocyclic nitrone **3e** (30%). FTIR (film): 3443 (N–H, O–H), 2994 (C–H), 2257 (C≡N), 1692 (C═N), 1198 (N–O), 1087 (C–O); ^{1}H NMR (CD_3OD): **2e** 70%: 1.36, 1.43 (2s, 6H, hydroxylamine $(CH_3)_2$), 1.75 (t, 2H, *J* 8 Hz, CH_2CH_2CN), 2.53 (t, 2H, *J* 8 Hz, CH_2CH_2CN), 3.75 (s, 4H, hydroxylamine $2OCH_2$); **3e** (30%): 1.34, 1.52 (2s, 6H, nitrone $(CH_3)_2$), 2.23 (t, 2H, *J* 8 Hz, nitrone C–CH_2CH_2), 2.70 (t, 2H, *J* 8 Hz, nitrone C–CH_2CH_2), 3.52 (d, 2H, *J* 11.5 Hz, nitrone O–CH_2–C–CH_2–O), 4.38 (d, 2H, *J* 11.5 Hz, nitrone O–CH_2–C–CH_2–O); MS, *m*/*z* (int.%): **2e** 167 (34), 149 (100), 132 (2), 113 (7), 57 (19); **3e** 184 (2), 169 (6), 153 (1), 112 (25), 96 (100), 69 (23); elemental analysis: found C 54.10, H 7.93, N 13.96, $C_9H_{16}N_2O_3$ requires C 53.99, H 8.08, N 13.99%.

*4.2.8. 2-Hydroxylamino-2-methylpropanenitrile (**2a**).* Compound **2a** via the Miller method.[24] Hydrocyanic acid (4 g, 4.4 mL, 0.148 mol) was cooled to 0 °C in a round bottom flask. (CAUTION! The reagent is extremely toxic and volatile (bp 26 °C), work only in an efficient fume hood). Water (1.2 mL) was added dropwise resulting 77% hydrocyanic acid and acetone oxime (6 g, 0.082 mol) was rapidly added with stirring. The reaction mixture was kept for five days at 6 °C and the HCN was carefully evaporated at rt under a mild nitrogen stream in a fume hood. The resulting semisolid was washed with pentane (2×10 mL) to remove unreacted acetone oxime and the residue was crystallized from 33% pentane/diethyl ether affording white needles, yield 2.25 g (27%). Mp 90–92 °C (lit.[24] 98–99 °C). FTIR and MS—see Section 4.2.1.

4.3. General procedure for oxidation of nitrones or hydroxylamines 2b, 2d, 3d, 2e and 3e to nitroso compounds 4b, 4d, 4e with sodium periodate (according to[5] with some modifications)

A solution of appropriate hydroxylamine or nitrone (1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL) was placed in a flask protected against light with aluminium foil. Then, a solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL) was slowly added with stirring at rt. In the case of β-hydroxylamino nitrile **2b**, the oxidation product was a blue oil (nitroso compound monomer). After 30 min, the reaction mixture was washed with hexane (10 mL×6), the combined organic layers dried over anhydrous magnesium sulfate and filtered, affording a blue solution of nitroso nitrile monomers. In case of all other compounds, the white solid precipitate of the oxidation product (nitroso nitrile dimer) was filtered off after 1 h (except compounds **2e** and **3e**—after 2 h), washed with water (5 mL×3) and dried in vacuum. The resulting grayish precipitate, containing some inorganic salts was washed with hot chloroform (50 °C, 5 mL×3) and filtered. The blue solution containing the appropriate nitroso nitrile monomer was filtered through a layer of silica gel for chromatography, and the solvent was removed in vacuum at rt, affording a deep blue oil of the nitroso compound monomer, that solidified quickly into the colourless dimer.

*4.3.1. 3-Methyl-3-nitrosobutanenitrile dimer (**4b**) (starting from hydroxylamine **2b** according to the general procedure).* A solution of 3-methyl-3-hydroxylaminobuta-nenitrile **2b** (222 mg, 1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL) was treated with a solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL). Yield 46 mg (21%), blue oil solidifying after recrystallization (10% chloroform/hexane), mp 59–62 °C (white plates). FTIR (KBr pellet): 2998 (C–H), 2250 (C≡N), 1262 (N_2O_2, nitroso dimer); ^{1}H NMR: 1.47 (s, 6H, $2CH_3$, monomer), 1.56 (s, 6H, $2CH_3$, dimer), 2.65 (s, 2H, CH_2); ^{14}N NMR:[12b] −576.95 (NO), 127.45 (CN); EIMS:[12a] *m*/*z* (int.%): 113 (0.2, MH^+), 112 (0.3, $M^{+\bullet}$), 82 (61, $[M-NO]^+$), 72 (22), 55 (100), 54 (38), 53 (11), 42 (13), 41 (40), 39 (36); elemental analysis: found C 53.48, H 7.39, N 25.15, calculated for $C_{10}H_{16}N_4O_2$, C 53.56, H 7.19, N 24.98%.

*4.3.2. 4-Methyl-4-nitrosopentanenitrile dimer (**4d**) (starting from nitrone **3d** according to the general procedure).* A solution of 5,5-dimethyl-1-oxy-4,5-dihydro-3*H*-pyrrol-2-ylamine **3d** (250 mg, 1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL) was treated with a solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL). Yield 86 mg (35%), grayish solid, mp 61–62 °C (white plates, 20% chloroform/hexane). FTIR (KBr pellet): 2990 (C–H), 2240 (C≡N), 1280 (N_2O_2, nitroso dimer); ^{1}H NMR: 1.47 (s, 6H, CH_3, monomer), 1.62 (s, 6H, CH_3, dimer), 2.23–2.47 (m, 4H, CH_2CH_2); ^{14}N NMR:[12b] −598.58 (NO), 131.45 (C≡N); EIMS, *m*/*z* (int.%):[12a] 127 (0.5, $MH^{+\bullet}$), 126 (0.1, $M^{+\bullet}$), 96 (53, $[M-NO]^+$), 69 (34), 68 (14), 57 (41), 56 (11), 55 (100), 54 (9), 53 (15), 42 (23), 41 (57), 39 (16); FIB-MS: 275 (27, $[2M+Na]^+$), 253 (67, $[2M+H]^+$); elemental analysis: found C 56.64, H 7.79, N 21.86, calculated for $C_{12}H_{20}N_4O_2$, C 57.12, H 7.99, N 22.20%.

*4.3.3. 5-(2-Cyanoethyl)-2,2-dimethyl-5-nitroso-1,3-dioxane dimer (**4e**) (starting from mixture of hydroxylamine **2e** and amino nitrone **3e** according to the general procedure).* A solution obtained in the procedure 4.2.5 mixture of 5-(2-cyano-ethyl)-2,2-dimethyl-5-hydroxylamine-1,3-dioxane (**2e**) and 2-amino-8,8-dimethyl-1-oxy-1-aza-7,9-dioxaspiro[4.5]dec-2-ene (**3e**) (390 mg, 1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL) was treated with a solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL). Yield 297 mg (77%), greyish solid, mp 56–58 °C (white plates, 33% chloroform/hexane). FTIR (KBr pellet): 2990 (C–H), 2247 (C≡N), 1278 (N_2O_2, nitroso dimer); ^{1}H NMR: 1.32, 1.43 (2s, 6H, $2CH_3$, monomer), 1.39, 1.40 (s, 6H, $2CH_3$, dimer), 2.11–2.29 (m, 4H, CH_2CH_2CN monomer), 2.35–2.58 (m, 4H, CH_2CH_2CN dimer), 3.87 (d, 2H, *J* 12.6 Hz, O–CH_2–C–CH_2–O monomer), 3.96 (d, 2H, *J* 12.9 Hz, O–CH_2–C–CH_2–O dimer), 4.55 (d, 2H, *J* 12.9 Hz, O–CH_2–C–CH_2–O dimer), 4.58 (d, 2H, *J* 12.6 Hz, O–CH_2–C–CH_2–O monomer); ^{14}N NMR:[12b] −595.78 (NO), 130.25 (C≡N); EIMS:[12a] *m*/*z* (int.%): 168 (8, $[M-NO]^+$), 153 (7), 111 (18), 110 (17), 82 (43), 80 (12), 59 (100), 55 (24), 54 (20), 53 (25), 43 (30), 41 (9); elemental

analysis: found C 53.91, H 7.17, N 14.53, calculated for $C_{18}H_{24}N_4O_6$, C 54.53, H 7.12, N 14.88%.

*4.3.4. 2-Methyl-2-nitrosopropanenitrile dimer (**4a**) (according to[29] with some modifications).* A cooled 0 °C solution of 2-hydroxylamino-2-methylpropanenitrile (**2a**) (0.56 g, 5.6 mmol) in water (6 mL) was saturated with gaseous chlorine with stirring during 5 min. The deep blue oil of monomer of α-nitroso nitrile precipitated and solidified into colourless solid. The crude compound was filtered off, washed with cold pentane (3 mL×2) and dried, affording white solid of 2-cyano-2-nitrosopropane dimer (**4a**), yield 0.51 g, 92%. Mp 48–49 °C (pentane), lit.[34] 53 °C. FTIR (KBr pellet): 2996 (C–H), 2244 (C≡N), 1296 (N_2O_2 nitroso dimer); ^{1}H NMR: 1.76 (s, 6H, $2CH_3$); ^{14}N NMR:[12b] −512.57 (NO), 117.96 (C≡N); MS, *m*/*z* (int.%):[12a] 98 (0.4, $M^{+\bullet}$), 68 (39, $[M-NO]^+$), 66 (12), 52 (18), 42 (25), 41 (100), 40 (8), 39 (33), 38 (6), 30 (23, NO^+).

*4.3.5. 5-Methyl-5-nitrosohexan-2-one dimer (**4c**) (according to[31] with some modifications).* To a cooled to 0 °C solution of 2,2,5-trimethyl-1-oxy-3,4-dihydro-2*H*-pyrrole (**3c**) (0.39 g, 3.07 mmol) in chloroform (10 mL), a solution of *m*-chloroperbenzoic acid (purity 85%, 0.69 g, 3.40 mmol) in chloroform was slowly added with stirring. The reaction mixture was stirred at 0 °C for next 2 h, diluted with chloroform (10 mL), and washed with 5% aqueous sodium hydroxide (10 mL×3) and water (10 mL×2). The organic phase was dried over anhydrous magnesium sulfate, and filtered through a short column filled with silica gel. The blue solution was concentrated affording a deep blue oil of the monomer that solidified into a colourless dimer of the *title compound* **4c** (0.29 g, 66%). Mp 58–60 °C (hexane), lit.[23] 53–55 °C. FTIR (KBr pellet): 2980 (C–H), 1720 (C=O), 1216 (N_2O_2 of nitroso compound dimer); ^{1}H NMR:[12b] 1.13 (s, 6H, $2CH_3$, monomer), 1,55 (s, 6H, $2CH_3$, dimer), 2.13 (s, 4H, CH_2CH_2, monomer and dimer), 2.28, 2.36 (2s, 3H, $COCH_3$, monomer and dimer); ^{14}N NMR:[12b] −604.71 (NO); MS, *m*/*z* (int.%):[23] 144 (1.5, MH^+), 113 (67), 95 (18), 55 (56), 43 (100).

Acknowledgements

The authors would like to express their gratitude to Dr. Jerzy Zakrzewski for valuable assistance.

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