Synthesis of tris(γ -oximinoalkyl)amines - new tripodal N4 ligands

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GENERAL INFORMATION

All reactions were performed in oven-dried (125 °C) glassware. Reactions were monitored by TLC on Merk silica TLC plates using UV, iodine on silica and solution of ninhydrin in MeOH for visualization. Commercial reagents (50% aqueous solution of NH₂OH, MeONH₂•HCl, BnONH₂•HCl, K₂CO₃, 10% palladium on activated charcoal, benzylamine) were used without additional purification. Methyl vinyl ketone was distilled in vacuo and stored in a freezer at -20 °C. Catalytic hydrogenation was performed in round-bottom Schlenk-type flasks equipped with a magnetic stirring bar and a balloon with hydrogen. Chromatography was performed using 40-60 μ m silica. NMR spectra were recorded on Bruker AM300 spectrometers with residual solvent peak as internal standard. HRMS spectra were obtained on Brucker Micro-TOFF instrument. Elemental analyses were performed in Analytical center of ZIOC RAS. Melting points (uncorrected) were determined on a Kofler hot stage microscope.

4-{Bis[3-(hydroxyimino)butyl]amino}-2-butanone oxime (7a)

To a solution of ammonia in methanol (2 M, 2 ml, 4 mmol) was added methyl vinyl ketone (1 ml, 12.3 mmol) with vigorous stirring. The reaction mixture was stirred for 15 min and then the

solution of hydroxylamine in methanol (0.75 ml of 50% aqueous solution, 12.3 mmol dissolved in 5 ml of methanol) was added. The reaction mixture was kept overnight at 2-5 °C and then for 72 h at -20 °C. White precipitate was filtered, washed with Et₂O and dried in vacuum (0.25 mm Hg). Yield: 435 mg (40%).

White solid, m.p. = 116-123 °C, mixture of isomers with ratio of *E*- and *Z*-fragments 1.2:1.

¹H (300 MHz, DMSO-d₆): δ = 1.73 and 1.76 [2 s, 9 H, (1), *E*- and *Z*-fragments], 2.23 and 2.37 [2 m, 6 H, (3), *E*- and *Z*-fragments], 2.60 [m, 6 H, (4)], 10.16 and 10.22 [2 s, 2 H, (6), *Z*- and *E*-fragments].

¹³C (75 MHz, DMSO-d₆): δ = 13.7 and 20.3 [(1), *E*- and *Z*-fragments], 26.0, 26.1, 33.3 and 33.4 [(3), *Z*-, *Z*-, *E*- and *E*-fragments], 48.7, 48.8 and 50.0 (4), 154.6 and 154.9 (2).

HRMS (+ve): For C₁₂H₂₅N₄O₃ [MH⁺] calculated m/z: 273.1921. Found: 273.1923.

Elemental analysis: for C₁₂H₂₄N₄O₃ calculated C: 52.92; H: 8.88; N: 20.57. Found: C: 52.89; H: 8.91; N: 20.46.

4-((Benzyl)[3-(hydroxyimino)butyl]amino)-2-butanone oxime (9)

Methyl vinyl ketone (2ml, 24 mmol) and benzylamine (1.3 ml, 12 mmol) were mixed neat with vigorous stirring. After 15 min the solution of hydroxylamine (1.65 ml of 50% aqueous solution, 27 mmol dissolved in 2 ml of methanol) was added. The reaction mixture was kept overnight at room temperature, the volatile components were evaporated and the residue was subjected to column chromatography [eluent hexane/EtOAc (3:1) → EtOAc/MeOH (10:1)]. Yield : 3.02 g (91%).

Colorless oil, mixture of 2 isomers (*EE*- and *EZ*-**9**) in ratio 8:1.

^1H (300 MHz, DMSO- d_6): *EE*-**9**, δ = 1.66 [s, 6 H, (1)], 2.27 [t, J = 7.0 Hz, 4 H, (3)], 2.58 [t, J = 7.0 Hz, 4 H, (4)], 3.54 [s, 2 H, (6)], 7.2-7.3 [m, 5 H, (8-10)], 10.0-10.2 [s br, 2 H, (5)]; characteristic signals of *EZ*-**9**, δ = 1.71 [s, 3 H, (1)], 2.45 [m, 2 H, (3)], 3.56 [s, 2 H, (6)].

^{13}C (75 MHz, DMSO- d_6): *EE*-**9**, δ = 13.7 (1), 33.0 (3), 50. (4), 57.6 (6), 127.2 (10), 128.5 and 129.1 (8 and 9), 139.9 (7), 154.6 (2)]; characteristic signals of *EZ*-**9**, δ = 20.1 [(1), Z-fragment], 25.6 [(3) Z-fragment], 48.9 [(4) Z-fragment], 159.9 [(2), Z-fragment].

HRMS (+ve): For $\text{C}_{15}\text{H}_{24}\text{N}_3\text{O}_2$ [MH^+] calculated m/z : 278.1863. Found: 278.1868.

4-[3-(Hydroxyimino)butylamino]-2-butanone oxime (10)

Bisoxime **9** (1.87 g) was dissolved in methanol (40 ml) and the vessel was filled with nitrogen. Catalyst (palladium on charcoal, 300 mg) was added and the reaction vessel was evacuated and filled with hydrogen 3 times. Hydrogenolysis was conducted for 45 min (until full conversion of starting material was observed by TLC). The catalyst was removed by centrifugation and volatile components were evaporated in vacuo. The residue was subjected to column chromatography [eluent EtOAc $\rightarrow$ EtOAc/MeOH (1:1)] and the product was dried in vacuo (0.25 Torr) until constant weight. Yield: 895 mg (71%).

Colorless oil, mixture of isomers with ratio of *E*- and *Z*-fragments 1.4:1.

^1H (300 MHz, DMSO- d_6): δ = 1.73 and 1.76 [2 s, 6 H, (1), *E*- and *Z*-fragments], 2.23 and 2.37 [2 t, J = 7.1 Hz, 6 H, (3), *E*- and *Z*-fragments], 2.65 [m, 6 H, (4)], 3.0-3.5 [s br, 1 H, (6)], 10.26 [s, 2 H, (5)].

^{13}C (75 MHz, DMSO- d_6): δ = 13.8 and 20.2 [(1), *E*- and *Z*-fragments], 29.2 and 36.0 [(3), *Z*- and *E*-fragments], 45.5 and 46.5 [(4), *Z*- and *E*-fragments], 154.6 (2).

HRMS (+ve): For $\text{C}_8\text{H}_{18}\text{N}_3\text{O}_2$ [MH^+] calculated m/z : 188.1394. Found: 188.1394.

4-{Bis[3-(hydroxyimino)butyl]amino}-2-butanone (11)

To a solution of compound **10** (200 mg, 1.09 mmol) in methanol (10 ml) was added methyl vinyl ketone (130 μl , 1.63 mmol) and the reaction mixture was kept overnight. The volatile components were removed in vacuo and the residue was subjected to column chromatography [eluent hexane/EtOAc (1:1) $\rightarrow$ EtOAc]. The product was dried in vacuo (0.25 Torr) until constant weight. Yield: 156 mg (56%).

Colorless oil, mixture of isomers with ratio of *E*- and *Z*-fragments 1:1.5.

^1H (300 MHz, DMSO- d_6): δ = 1.73 and 1.76 [2 s, 6 H, (1), *E*- and *Z*-fragments], 2.08 [s, 3 H, (9)], 2.23 and 2.35 [2 m, 6 H, (3), *E*- and *Z*-fragments], 2.56 [m, 6 H, (4 and 6)], 2.67 [t, J = 6.8 Hz, (7)], 10.1-10.4 [s br, 2 H, (5)].

^{13}C (75 MHz, DMSO- d_6): δ = 13.6 and 20.2 [(1), *E*- and *Z*-fragments], 25.7, 25.8 and 33.1 [(3), *Z*-, *Z*- and *E*-fragments], 30.2 (9), 40.1 (7), 46.3, 47.8, 47.9, 48.7 and 50.0 (4 and 6), 154.6 and 154.8 [(2), *E*- and *Z*-fragments], 208.1 (8).

HRMS (+ve): For $\text{C}_{12}\text{H}_{24}\text{N}_3\text{O}_3$ [MH^+] calculated m/z : 258.1812. Found: 258.1819.

4-[[3-(Hydroxyimino)butyl][3-(methoxyimino)butyl]amino}-2-butanone oxime (7b)

To a solution of compound **11** (65 mg, 0.25 mmol) in methanol (3 ml), MeONH₂•HCl (25 mg, 0.3 mmol) and potassium carbonate (42 mg, 0.3 mmol) were added. The reaction mixture was stirred for 3 h and the volatile components were removed in vacuo. The residue was subjected to column chromatography [eluent hexane/EtOAc (3:1) → EtOAc/MeOH (10:1)] and the product was dried in vacuo (0.25 Torr) until constant weight. Yield: 59 mg (83%).

White foam, mixture of isomers with ratio of *E*- and *Z*-fragments 1:1.2.

¹H (300 MHz, DMSO-*d*₆): δ = 1.73, 1.75, 1.76 and 1.78 [4 s, 9 H, (1 and 9)], 2.23 and 2.37 [2 s, 6 H, (3 and 7), *E*- and *Z*-fragments], 2.58 [m, 6 H, (4 and 6)], 3.69 and 3.70 [2 s, 3 H, (10)], 10.18 and 10.24 [2 s, 2 H, (5), *E*- and *Z*-fragments].

¹³C (75 MHz, DMSO-*d*₆): δ = 13.6, 14.1, 20.0 and 20.1 [(1 and 9), *E*-, *E*-, *Z*- and *Z*-fragments], 25.6, 25.8, 26.5, 26.6, 33.0, 33.2 [(3 and 7), *Z*-, *Z*-, *Z*-, *E*- and *E*-fragments], 48.6 and 49.7 [(4 and 6), *Z*- and *E*-fragments], 154.5, 154.7, 154.8, 156.2 and 156.7 (2 and 8).

HRMS (+ve): For C₁₃H₂₇N₄O₃ [MH⁺] calculated *m/z*: 287.2078. Found: 287.2071.

N-benzyl-3-(hydroxyimino)butan-1-amine (**12**)

To benzylamine (0.5 ml, 4.6 mmol) was added methyl vinyl ketone (0.37 ml, 4.6 mmol) and the reaction mixture was stirred for 10 min. Then solution of hydroxylamine (0.28 ml of 50% aqueous solution, 4.6 mmol dissolved in 1.5 ml of methanol) was added. The reaction mixture was kept overnight and volatile components were removed in vacuo. The residue was subjected to column chromatography and the product was dried in vacuo (0.25 Torr) until constant weight. Yield: 560 mg (64%).

White solid, mp = 68-74 °C (lit. 47-49 °C¹), mixture of 2 isomers (*E*- and *Z*-**12**) in ratio 1:1.3.

¹H (300 MHz, DMSO-*d*₆): *E*-**12**, δ = 1.73 [s, 3 H, (1)], 2.28 [t, *J* = 6.9 Hz, 2 H, (3)]; *Z*-**12**, δ = 1.77 [s, 3 H, (1)], 2.44 [t, *J* = 6.9 Hz, 2 H, (3)]; signals of both isomers, δ = 2.64 [m, 2 H, (4)], 3.69 [s, 2 H, (6)], 7.1-7.4 [m, 5 H, (8-10)], 10.29 [s, 1 H, (5)].

¹³C (75 MHz, DMSO-*d*₆): *E*-**12**, δ = 13.4 (1), 35.6 (3), 45.6 (4); 154.2 (2); *Z*-**12**, δ = 19.6 (1), 28.7 (3), 44.7 (4), 154.5 (2); signals of both isomers, δ = 52.6 (6), 126.4 (10), 127.8 and 128.0 (8 and 9), 140.9 (7).

Elemental analysis: for C₁₁H₁₆N₂O calculated C: 68.72; H: 8.39; N: 14.57. Found: C: 68.52; H: 8.98; N: 14.23.

4-((Benzyl)[3-(hydroxyimino)butyl]amino)-2-butanone (**13**)

To a solution of compound **12** (560 mg, 2.9 mmol) in methanol (4 ml) methyl vinyl ketone (0.28 ml, 3.48 mmol) was added. The reaction mixture was stirred for 2 h, volatile components were removed in vacuo and the residue was subjected to column chromatography [eluent hexane/EtOAc (3:1) → EtOAc]. The resulted yellow oil was dried in vacuo (0.25 Torr) until constant weight. Yield: 547 mg (72%).

Colorless viscous oil, mixture of 2 isomers (*E*- and *Z*-**13**) in ratio 1.7:1.

¹H (300 MHz, DMSO-*d*₆): *E*-**13**, δ = 1.66 [s, 3 H, (1)], 2.03 [s, 3 H, (11)], 2.25 [t, *J* = 6.9 Hz, 2 H, (3)], 3.51 [s, 2 H, (6)], 10.2 [s, 1 H, (5)]; *Z*-**13**, δ = 1.70 [s, 3 H, (1)], 2.02 [s, 3 H, (11)], 2.42

¹ Gnichtel, H., Gau, B. P. *Liebigs Ann. Chem.*, **1982**, 12, 2223

[t, $J = 6.9$ Hz, 2 H, (3)], 3.53 [s, 2 H, (6)], 10.1 [s, 1 H, (5)]; signals of both isomers, $\delta = 2.5$ -2.6 [m, 4 H, (4 and 14)], 2.66 [m, 2 H, (13)], 7.2-7.4 [m, 5 H, (8-10)].

^{13}C (75 MHz, DMSO- d_6): *E*-**13**, $\delta = 13.2$ (1), 32.6 (3), 47.7 (4); *Z*-**13**, $\delta = 19.7$ (1), 25.2 (3), 48.6 (4); signals of both isomers, $\delta = 29.7$ (11), 40.5 (13), 49.6 (14), 57.3 (6), 126.7 (10), 128.1 and 128.7 (8 and 9), 139.3 (7), 154.1 (2), 208.0 (12).

HRMS (+ve): For $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_2$ [MH^+] calculated m/z : 263.1754. Found: 263.1748.

4-((Benzyl)[3-(methoxyimino)butyl]amino)-2-butanone oxime (14)

To a solution of compound **13** (510 mg, 1.95 mmol) in methanol (4 ml) $\text{MeONH}_2 \cdot \text{HCl}$ (195 mg, 2.34 mmol) and potassium carbonate (325 mg, 2.34 mmol) were added. The reaction mixture was stirred for 18 h. Volatile components were removed in vacuo and the residue was subjected to column chromatography [eluent hexane/EtOAc (1:1) $\rightarrow$ EtOAc]. The resulted oil was dried in vacuo (0.25 Torr) until constant weight. Yield: 498 mg (88%).

Colorless viscous oil, mixture of isomers with ratio of *E*- and *Z*-fragments 1.9:1.

^1H (300 MHz, DMSO- d_6): $\delta = 1.67$, 1.68, 1.71 and 1.72 [4 s, 6 H, (1 and 11)], 2.28 and 2.46 [2m, 4 H, (3 and 13), *E*- and *Z*-fragments], 2.56 [m, 4 H, (4 and 14)], 3.53 and 3.56 [2 s, 2 H, (6)], 3.65 and 3.69 [2 s, 3 H, (15), *Z*- and *E*-fragments], 7.2-7.3 [m, 5 H, (8-10)], 10.20, 10.25 and 10.26 [3 s, 1 H, (5), *Z*-, *E*- and *E*-fragments].

^{13}C (75 MHz, DMSO- d_6): $\delta = 13.2$, 13.7, 19.5 and 19.6 [(1 and 11), *E*-, *E*-, *Z*- and *Z*-fragments], 25.2, 25.3, 25.8, 25.9, 32.5 and 32.6 [(3 and 13), *Z*-, *Z*-, *Z*-, *Z*-, *E*- and *E*-fragments], 48.4, 49.3 and 49.5 (4 and 14), 57.0 (6), 60.6 (15), 126.8 (10), 128.0 and 128.7 (8 and 9), 139.3 and 139.5 (7), 154.1, 154.4, 155.9 and 156.4 (2 and 12).

HRMS (+ve): For $C_{16}H_{26}N_3O_2$ $[MH^+]$ calculated m/z : 292.2020. Found: 292.2032.

4-[3-(Methoxyimino)butylamino]-2-butanone oxime (15)

Compound **8** (250 mg, 0.86 mmol) was dissolved in methanol (10 ml) and the flask was filled with nitrogen. Catalyst (palladium on charcoal, 50 mg) was added and the reaction vessel was evacuated and filled with hydrogen 3 times. Hydrogenolysis was conducted for 20 min. The catalyst was removed by centrifugation and volatile components were evaporated in vacuo. The residue was subjected to column chromatography [eluent hexane/EtOAc (1:1) $\rightarrow$ EtOAc/MeOH (5:1)] and the product was dried in vacuo (0.25 Torr) until constant weight. Yield: 160 mg (92%).

Colorless viscous oil, mixture of isomers with ratio of *E*- and *Z*-fragments 3.7:1.

1H (300 MHz, DMSO- d_6): δ = 1.73, 1.75, 1.76 and 1.79 [4 s, 6 H, (1 and 10)], 2.23 and 2.37 [2 t, J = 6.9 Hz, J = 7.0 Hz, (3 and 8), 4 H *E*- and *Z*-fragments], 2.66 [m, 4 H, (4 and 7)], 3.69 and 3.71 [2 s, 3 H, (11), *Z*- and *E*-fragments], 10.1-10.4 [s br, 1 H, (5)].

^{13}C (75 MHz, DMSO- d_6): δ = 13.2, 13.8, 19.5 and 19.7 [(1 and 10), *E*-, *E*-, *Z*- and *Z*-fragments], 28.7, 29.3, 35.4 and 35.7 [(3 and 8), *Z*-, *Z*-, *E*- and *E*-fragments], 45.0, 45.7, 45.8 and 46.0 (4 and 7), 60.5 (11), 154.1, 154.3, 155.8 and 156.4 (2 and 9).

HRMS (+ve): For $C_9H_{20}N_3O_2$ $[MH^+]$ calculated m/z : 202.1550. Found: 202.1549.

4-{[3-(Hydroxyimino)butyl][3-(methoxyimino)butyl]amino}-2-butanone (16)

To a solution of **15** (150 mg, 0.74 mmol) in methanol (2 ml) was added methyl vinyl ketone (75 μ l, 0.89 mmol). The reaction mixture was stirred for 5 h. Volatile components were removed in

¹H (300 MHz, DMSO-d₆): δ = 1.74, 1.76 and 1.78 [3 s, 6 H, (1 and 6)], 2.09 [s, 3 H, (10)], 2.23 and 2.36 [2 m, (4 H, (3 and 8), *E*- and *Z*-fragments)], 2.56 [m, 6 H, (4, 9 and 13)], 2.67 [m, 2 H, (12)], 3.78 [s, 3 H, (15)], 10.23 [s br, 1 H, (14)].

HRMS (+ve): For $C_{13}H_{26}N_3O_3$ $[MH^+]$ calculated m/z: 272.1968. Found: 272.1961.

To a solution of compound **16** (95 mg, 0.35 mmol) in methanol (2 ml) $\text{BnONH}_2 \cdot \text{HCl}$ (67 mg, 0.42 mmol) and potassium carbonate (58 mg, 0.42 mmol) were added. The reaction mixture was stirred for 20 h. Volatile components were removed in vacuo and the residue was subjected to column chromatography [eluent hexane/EtOAc (5:1) $\rightarrow$ EtOAc]. The resulted oil was dried in vacuo (0.25 Torr) until constant weight. Yield: 80 mg (61%).

White foam, mixture of isomers with ratio of *E*- and *Z*-fragments 1:1.

^1H (300 MHz, DMSO- d_6): δ = 1.7-1.8 [m, 9 H, (1, 6 and 10)], 2.23 and 2.38 [2 m, 6 H, (3, 8 and 12), *E*- and *Z*-fragments], 2.58 [m, 6 H, (3, 9, and 13)], 3.69 [m, 3 H, (15)], 4.98 and 5.00 [2 s, 2 H, (16)], 7.2-7.4 [m, 5 H, (18, 19 and 20)], 10.20 and 10.25 [2 s, 1 H, (14)].

^1H (300 MHz, DMSO- d_6): δ = 13.2, 13.8, 14.0, 19.6 and 19.8 [(1, 6 and 10), *E*-, *E*-, *E*-, *Z*- and *Z*-fragments], 25.3, 25.4, 25.5, 26.0, 26.1, 26.2 and 26.4 [(3, 8 and 12), *Z*-fragments], 32.6, 32.7 and 32.8 [(3, 8 and 12), *E*-fragments], 48.2, 49.3 and 49.5 (4, 9 and 13), 60.5 (15), 74.3 and 74.4 (16), 127.4, 127.6 and 128.2 (18, 19 and 20), 138.4 (17), 154.1, 154.4, 155.8, 156.5 and 157.0 (2, 7 and 11).

HRMS (+ve): For $\text{C}_{20}\text{H}_{33}\text{N}_4\text{O}_3$ $[\text{MH}^+]$ calculated m/z : 377.2547. Found: 377.2552.

4-{Bis[3-(hydroxyimino)butyl]amino}-2-butanone oxime (7a)

4-[(Benzyloxy)butyl]amino-2-butanone oxime (9)

4-[3-(Hydroxyimino)butylamino]-2-butanone oxime (10)

4-{Bis[3-(hydroxyimino)butyl]amino}-2-butanone (11)

4-{[3-(Hydroxyimino)butyl][3-(methoxyimino)butyl]amino}-2-butanone oxime (7b)

N-benzyl-3-(hydroxyimino)butan-1-amine (12)

4-{{(Benzyl)[3-(hydroxyimino)butyl]amino}-2-butanone (13)

4-{{(Benzyl)[3-(methoxyimino)butyl]amino}-2-butanone oxime (14)

4-[3-(Methoxyimino)butylamino]-2-butanone oxime (15)

4-{[3-(Hydroxyimino)butyl][3-(methoxyimino)butyl]amino}-2-butanone (16)

Chemical structure of compound 10 is shown in the top left. The ^1H NMR spectrum (CDCl₃) is displayed below, with peaks labeled by their chemical shift (ppm) and integration values.

Chemical shift (ppm): 10.25, 7.32, 7.30, 5.00, 4.98, 3.70, 3.69, 3.68, 3.34, 2.58, 2.55, 2.50, 2.38, 2.35, 2.34, 2.24, 2.23, 2.22, 1.81, 1.80, 1.77, 1.75, 1.74, 1.73, 1.70.

Integration values: 9.043, 48.740, 19.562, 29.612, 25.595, 96.721.