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Facile Synthesis of Flexible Bis(pyrazol-1-yl)alkane and Related Ligands in a Superbasic Medium

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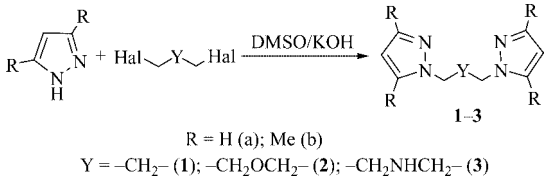
Flexible ligands 1,3-bis(pyrazol-1-yl)propanes, bis[2-(pyrazol-1-yl)ethyl] ethers, and bis[2-(3,5-dimethylpyrazol-1-yl)-ethyl]amine were prepared by a facile procedure involving the reaction of pyrazoles with 1,3-dibromopropane, bis(2-chloroethyl) ether or bis(2-chloroethyl)amine hydrochloride in a superbasic medium (dimethyl sulfoxide/potassium hydroxide). Reaction of bis(2-chloroethyl)amine and pyrazole unexpectedly led to 1,4-bis[2-(pyrazol-1-yl)ethyl]piperazine. The corresponding 4,4′-diiodo-substituted bis(pyrazole) derivatives were prepared by oxidative iodination with $I_2/HIO_3/H_2SO_4$ in acetic acid. Vilsmeier–Haak formylation of some of the prepared compounds yielded the corresponding dialdehydes.

Introduction

Complexes of heterocyclic chelating ligands with transition metals often mimic various metalloenzymes, which assists in the elucidation of their structure and action. Bis(pyrazol-1-yl)alkanes and related compounds are among such ligands. The first ligands containing a methylene bridge between two pyrazole rings were prepared by Trofimenko in 1970.[1] Since then bis(pyrazol-1-yl)methanes and 1,2-bis(pyrazol-1-yl)ethanes have received much attention in relation to their coordination chemistry; hundreds of their complexes with transition metals and main group elements were prepared and characterized.[2] Ligands with longer and thus more flexible bridges between the pyrazole rings, for example 1,3-bis(pyrazol-1-yl)propanes, were also reported, but only a few of their coordination compounds were prepared.[3]

The next generation of chelating bis(pyrazole) ligands is represented by compounds possessing a spacer unit containing additional donor heteroatoms, namely oxygen, nitrogen, or sulfur. This group of ligands derived from 3,5-dimethylpyrazole was first introduced by Sorrell.[4] Subsequently, copper(II) and zinc complexes with ligands of this type were considered as biomimetic models of hemocyanin, carbonic anhydrase, thermolysin, alcohol dehydrogenase, and other metalloproteins.[5] Very recently, reports on the application of nickel(II), aluminum, and zinc complexes of **2b** and **3b** (Scheme 1) as efficient olefin oligomerization and polymerization catalysts appeared.[6]



Scheme 1.

However, bis(pyrazole) ligands with flexible and heteroatom-containing spacers are much less investigated relative to bis(pyrazol-1-yl)methanes. This is probably due to complicated procedures for the preparation of such compounds. Thus, the synthetic protocol developed by Sorrell involves prolonged heating of sodium pyrazolides with bis(2-chloroethyl) ether or bis(2-chloroethyl)amine in DMF or THF, which leads to experimental difficulties from dealing with toxic and air- and moisture-sensitive sodium hydride in absolutely dry solvents.[4] Propane derivatives **1a**,**b** (Scheme 1) were prepared similarly by using potassium *tert*-butoxide as the base instead of sodium hydride.[3] The use of strong bases is probably explained by the low reactivity of dihalide derivatives in nucleophilic substitution.

As it is known form the literature, the use of superbasic media often permits nucleophilic substitution reactions that only proceed sluggishly under regular conditions. Herein we report the use of superbasic medium DMSO–KOH for the synthesis of some bis(pyrazole) ligands.

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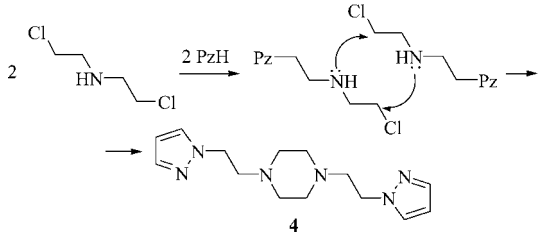
Results and Discussion

The reaction between pyrazole or 3,5-dimethylpyrazole and 1,3-dibromopropane occurred readily at room temperature to give corresponding 1,3-bis(pyrazol-1-yl)propanes **1a**,**b** in good yields (Scheme 1).

Ligands containing oxygen or nitrogen donor heteroatoms in the spacer unit connecting two pyrazole rings were prepared in the same manner by using bis(2-chloroethyl)-ether or bis(2-chloroethyl)amine hydrochloride as the starting dihalide derivatives. Naturally, the chloride derivatives were less reactive than 1,3-dibromopropane. Besides, their reactivity in nucleophilic substitution reactions is further suppressed by the presence of electron-withdrawing oxygen or nitrogen atoms. Nevertheless, by raising the reaction temperature to 80–100 °C heteroatom-containing bis(pyrazole) ligands **2a**,**b** and **3b** were obtained in satisfactory-to-good yields. It should be noted that the addition of a 20–50% excess of the less reactive bis(2-chloroethyl) ether or the bis(2-chloroethyl)amine derivatives was required to achieve full conversion of the starting pyrazole.

When unsubstituted pyrazole was treated with 20% excess of bis(2-chloroethyl)amine in conditions analogous to the synthesis of 3,5-dimethyl derivative **3b**, 1,4-bis[2-(pyrazol-1-yl)ethyl]piperazine **4** was isolated unexpectedly in 85% yield. The formation of this product can be explained by intermolecular self-alkylation of the pyrazole-containing intermediate leading to product **4** instead of expected **3a** (Scheme 2). In case of 3,5-dimethylpyrazole, the self-alkylation step is probably hindered by steric factors.

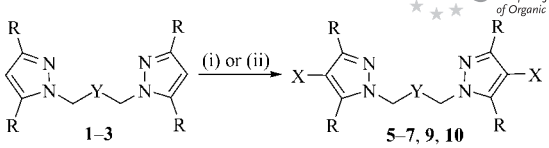


Scheme 2.

The coordination properties of bis(pyrazol-1-yl)alkanes may be varied widely by introducing substituents into the pyrazole rings.[2] Usually this was achieved by the synthesis of alkyl-substituted ligands,[7] but only a few functional derivatives, such as 4,4′-dinitro-,[8] 4,4′-dichloro-,[9] and 4,4′-dibromo-substituted[8] bis(pyrazol-1-yl)methanes were reported.

We prepared 4,4′-diiodo derivatives of bis(pyrazole) compounds **1**–**4** described above. The iodide functionality was chosen because of its lability in substitution reactions by other functional groups.[10] Oxidative iodination of the pyrazole ring was achieved by $I_2/HIO_3/H_2SO_4$ in acetic acid (Scheme 3).

Iodination of compounds **1**–**3** provided corresponding diiodo derivatives **5**–**7** in good yields. When the reaction was carried out with unsubstituted bis(pyrazole)s, the iodine atoms were introduced regioselectively into the 4-position of the pyrazole rings; no other products were isolated.

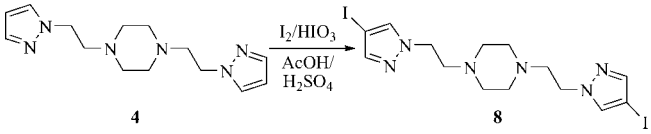


(i) $I_2/HIO_3/H_2SO_4/AcOH$
(ii) $POCl_3/DMF$
R = H (a); Me (b) X = I (**5**–**7**); CH=O (**9**, **10**)
Y = $–CH_2–$ (**1**, **5**, **9**); $–CH_2OCH_2–$ (**2**, **6**, **10**); $–CH_2NHCH_2–$ (**3**, **7**)

Scheme 3.

Such selectivity in I_2/HIO_3 iodination reactions was reported previously for other pyrazole derivatives.[11]

Similarly, iodination of piperazine derivative **4** gave 4,4′-diiodo-substituted **8** in 81% yield (Scheme 4).



Scheme 4.

Another reactive substituent, namely the formyl group, was introduced into the pyrazole rings of compounds **1b** and **2b** by Vilsmeier–Haak formylation (Scheme 3). Corresponding dialdehydes **9b** and **10b** were isolated readily in high yields.

To obtain some preliminary information on the complexing ability of the synthesized ligands, we prepared their coordination compounds with zinc(II) chloride and copper(II) nitrate. Thus, propane derivative **1b** reacts with $ZnCl_2$ in diethyl ether (metal-to-ligand ratio 1:1) to give a solid adduct. This complex is moderately soluble in acetone and ethanol and has a sharp melting point, which reveals that it has a nonpolymeric structure. In the ^{13}C NMR spectrum of the complex there is only one set of signals. The signals of the pyrazole ring are shifted downfield, whereas those of the trimethylene bridge are shifted upfield, which indicates the transfer of the electronic density from the chelating ligand to the formed metallocycle.

Ligand **2b** with a heteroatom-containing spacer reacts with one equivalent of $Cu(NO_3)_2·3H_2O$ to yield a crystalline solid. The structure of this complex was investigated by means of IR spectroscopy. Two strong bands corresponding to asymmetric N–O vibrations in the nitrate ions (ν_3) were detected in the IR spectra of the complex at 1482 and 1290 cm^{-1}. The split value $\Delta\nu_3$ of 192 cm^{-1} and absence of other ν_3 bands suggests a bidentate coordination mode for both nitrate ions.[12] The bands of pyrazole ring vibrations (1555, 1430 cm^{-1}) are shifted relative to the same bands in the spectra of the free ligand as is the stretching C–O vibration band at 1102 cm^{-1}. Displacements of the bands are fairly significant and indicate a N,N,O-tridentate coordination of ligand **2b**.

A detailed report on the complexing properties of bis(pyrazole) ligands, including X-ray structure analysis and biological activity assay is currently under preparation and will be published elsewhere.

Conclusions

In summary, we propose a facile procedure for the synthesis of bis(pyrazol-1-yl)alkanes and related ligands. This new synthetic route does not require manipulations with toxic and flammable alkali metal hydrides and simplifies isolation of pure products, making them readily available compounds. In a preliminary complexation probe of bis(pyrazole) ligands with transition metals, 1,3-bis(3,5-dimethylpyrazol-1-yl)propane formed an eight-membered ring chelate, whereas 2,2′-bis(3,5-dimethylpyrazol-1-yl)ethyl ether acted as a N,N,O-tridentate ligand.

Experimental Section

Elemental analyses were carried out with a Carlo Erba analyzer. IR spectra of solid samples as KBr pellets and of thin layers (0.1 mm) for liquids were recorded with Nicolet 5700 spectrophotometer. NMR spectra were recorded with a Bruker AV300 instrument. Mass spectra were registered with a TRACE DSQ (Thermo Electron Corporation, USA) instrument. Assignments of the NMR methylene signals for compounds **2a**,**b**, **3b**, and **4** were made according to ChemDraw estimation on the basis of group increments.

General Procedure for the Synthesis of Bis(pyrazole) Compounds: A suspension of pyrazole or 3,5-dimethylpyrazole (20 mmol) and finely powdered KOH (2.24 g, 40 mmol) in DMSO (15 mL) was vigorously stirred for 1 h at 80 °C. The corresponding dihalide derivative (10 mmol) dissolved in DMSO (10 mL) was then added dropwise over 30 min [for compound **3b**, bis(2-chloroethyl)amine hydrochloride was used; in this case additional KOH (0.56 g, 10 mmol) was introduced into the reaction mixture to convert the salt into the free base]. Stirring was continued until completion of the reaction (TLC control), and the reaction mixture was poured into water (250 mL) and extracted with chloroform (6 × 30 mL). The extract was washed with water (2 × 20 mL) and dried with anhydrous calcium chloride. After removal of the solvent, products **1**–**3** were purified by crystallization or vacuum distillation.

1,3-Bis(pyrazol-1-yl)propane (1a): Yield: 1.09 g (62%) as a colorless liquid. B.p. 134–136 °C (5 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (quintet, J = 6.5 Hz, 2 H, $CH_2CH_2CH_2$), 4.05 (t, J = 6.5 Hz, 4 H, pz-CH_2), 6.21 (t, J = 2 Hz, 2 H, 4-H-pz), 7.25 (d, J = 2 Hz, 2 H, 3-H-pz), 7.49 (d, J = 2 Hz, 2 H, 5-H-pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.6 ($CH_2CH_2CH_2$), 48.3 (pz-CH_2), 105.2 (4-C-pz), 129.4 (5-C-pz), 139.3 (3-C-pz) ppm. IR (thin film): $\tilde{\nu}$ = 1500, 1440 (ν_{Pz}), 1270 (βCH), 1040 (Pz ring breathing) cm^{-1}. $C_9H_{12}N_4$ (176.22): calcd. C 61.34, H 6.86, N 31.79; found C 60.95, H 6.86, N 31.55.

1,3-Bis(3,5-dimethylpyrazol-1-yl)propane (1b): Yield: 5.51 g (91%) as colorless crystals. M.p. 71–72 °C (benzene/hexane, 1:1). ^{1}H NMR (300 MHz, C_6D_6): δ = 1.84 (s, 6 H, 3-Me-pz), 2.32 (quintet, J = 6 Hz, 2 H, $CH_2CH_2CH_2$), 2.93 (s, 6 H, 5-Me-pz), 3.71 (t, J = 6 Hz, 4 H, pz-CH_2), 5.78 (s, 2 H, 4-H-pz) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 11.0 (5-Me-pz), 14.5 (3-Me-pz), 30.8 ($CH_2CH_2CH_2$), 48.0 (pz-CH_2), 105.2 (4-C-pz), 139.5 (5-C-pz), 147.5 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1530, 1410 (ν_{Pz}), 1300 (βCH), 1010 (Pz ring breathing), 750 (β_{Pz}) cm^{-1}. $C_{13}H_{20}N_4$ (232.32): calcd. C 67.21, H 8.68, N 24.12; found C 67.03, H 8.51, N 24.02.

Bis[2-(pyrazol-1-yl)ethyl] Ether (2a): Yield: 2.42 g (59%) as a colorless liquid. B.p. 107–108 °C (5 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (t, J = 5 Hz, 4 H, OCH_2CH_2pz), 4.14 (t, J = 5 Hz, 4 H, OCH_2CH_2Pz), 6.12 (t, J = 2 Hz, 2 H, 4-H-pz), 7.21 (d, J = 2 Hz, 2 H, 3-H-pz), 7.41 (d, J = 2 Hz, 2 H, 5-H-pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0 (OCH_2CH_2pz), 69.8 (OCH_2CH_2pz), 105.5 (4-C-pz), 130.1 (5-C-pz), 139.4 (3-C-pz) ppm. IR (thin film): $\tilde{\nu}$ = 1510, 1440 (ν_{Pz}), 1360 (βCH), 1090 (C–O), 1040 (Pz ring breathing), 940 (γCH), 740 (β_{Pz}) cm^{-1}. $C_{10}H_{14}N_4O$ (206.24): calcd. C 58.24, H 6.84, N 27.17; found C 58.40, H 6.91, N 27.50.

Bis[2-(3,5-dimethylpyrazol-1-yl)ethyl] Ether (2b): Yield: 7.48 g (98%) as colorless crystals. M.p. 89.5–90 °C (*i*PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 6 H, 3-Me-pz), 2.28 (s, 6 H, 5-CH_3-pz), 3.38 (t, J = 5 Hz, 4 H, OCH_2CH_2pz), 3.63 (t, J = 5 Hz, 4 H, OCH_2CH_2Pz), 5.68 (s, 2 H, 4-H-pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1 (5-Me-pz), 13.6 (3-Me-pz), 48.4 (OCH_2CH_2pz), 70.4 (OCH_2CH_2pz), 104.9 (4-C-pz), 139.8 (5-C-pz), 147.7 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1552, 1407 (ν_{Pz}), 1348 (βCH), 1113 (C–O), 1020 (Pz ring breathing), 980 (γCH), 772 (β_{Pz}) cm^{-1}. $C_{14}H_{22}N_4O$ (262.35): calcd. C 64.09, H 8.45, N 21.36; found C 63.77, H 8.67, N 21.35.

Bis[2-(3,5-dimethylpyrazol-1-yl)ethyl]amine (3b): Yield: 1.46 g (56%) as colorless crystals. M.p. 81.5–82 °C (benzene/hexane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 6 H, 3-Me-pz), 2.21 (s, 6 H, 5-CH_3-pz), 2.97 (t, J = 6 Hz, 4 H, NCH_2CH_2pz), 4.02 (t, J = 6 Hz, 4 H, NCH_2CH_2Pz), 5.76 (s, 2 H, 4-H-pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5 (5-Me-pz), 14.0 (3-Me-pz), 48.2 (NCH_2CH_2pz), 49.2 (NCH_2CH_2pz), 105.0 (4-C-pz), 140.0 (5-C-pz), 147.3 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 4250 (N–H), 3300 (br.) (N–H, hydrogen-bonded), 1550 (ν_{Pz}), 1300 (βCH), 1030 (Pz ring breathing), 930 (γCH), 760 (β_{Pz}) cm^{-1}. MS (EI): *m*/*z* (%) = 262 (2) [M + H]$^+$, 165 (25) [M – PzH]$^+$, 152 (48) [M – $PzCH_2$]$^+$, 123 (7) [$PzCH_2CH_2$]$^+$, 109 (60) [$PzCH_2$]$^+$, 97 (100) [PzH + H]$^+$. $C_{14}H_{23}N_5$ (261.37): calcd. C 64.34, H 8.87, N 26.80; found C 63.97, H 8.70, N 26.44.

1,4-Bis[2-(pyrazol-1-yl)ethyl]piperazine (4): A suspension of pyrazole (3.4 g, 50 mmol) and finely powdered KOH (5.6 g, 100 mmol) in DMSO (15 mL) was vigorously stirred for 1 h at 80 °C. A mixture of bis(2-chloroethyl)amine hydrochloride (4.46 g, 25 mmol) and KOH (1.4 g, 25 mmol) in DMSO (15 mL) was then added dropwise over 30 min at room temperature. Stirring was continued for 24 h and then an additional portion of bis(2-chloroethyl)amine hydrochloride (0.89 g, 5 mmol) and KOH (0.28 g, 5 mmol) was introduced into the reaction mixture. Stirring was continued for another 24 h, and then the reaction mixture was poured into water (300 mL) and extracted with chloroform (6 × 30 mL). The extract was washed with water (2 × 20 mL), dried with anhydrous calcium chloride, and concentrated in vacuo to give colorless crystals of compound **4** [3.49 g, 85% based on bis(2-chloroethyl)amine]. M.p. 111–112 °C (*i*PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 8 H, piperazine ring-CH_2), 2.80 (t, J = 7 Hz, 4 H, NCH_2CH_2pz), 4.23 (t, J = 7 Hz, 4 H, NCH_2CH_2Pz), 6.22 (t, J = 2 Hz, 2 H, 4-H-pz) 7.44 (d, J = 2 Hz, 2 H, 3-H-pz), 7.48 (d, J = 2 Hz, 2 H, 5-H-pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.7 (NCH_2CH_2pz), 53.1 (piperazine ring, CH_2), 57.8 (NCH_2CH_2Pz), 105.3 (4-C-pz), 128.7 (5-C-pz), 139.1 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1620, 1460 (ν_{Pz}), 1000 (Pz ring breathing), 710 (β_{Pz}) cm^{-1}. $C_{14}H_{22}N_6$ (274.36): calcd. C 61.29, H 8.08, N 30.63; found C 61.04, H 8.03, N 30.35.

General Oxidative Iodination Procedure: A suspension of compound **1**–**4** (20 mmol), powdered iodine (4.06 g, 16 mmol), and HIO_3 (1.41 g, 8 mmol) in glacial acetic acid (30 mL) and aqueous H_2SO_4 (30%, 3 mL) was vigorously stirred in a hot water bath set at 100 °C until the reaction mixture became colorless. The mixture was then poured into water (250 mL), the precipitate was filtered, or, in case when no precipitate was formed, extracted with chloro-

form (5 × 30 mL). After drying or removal of the solvent diiodo derivatives **5**–**8** were purified by crystallization or vacuum distillation.

1,3-Bis(4-iodopyrazol-1-yl)propane (5a): Yield: 0.338 g (79%) as colorless crystals. M.p. 62–64 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (quintet, J = 6 Hz, 2 H, $CH_2CH_2CH_2$), 4.10 (t, J = 6 Hz, 4 H, pz-CH_2), 7.44 (s, 2 H, 3-H-pz), 7.51 (s, 2 H, 5-H-pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.7 ($CH_2CH_2CH_2$), 49.0 (pz-CH_2), 56.2 (4-C-pz), 129.6 (5-C-pz), 144.7 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1460 (ν_{Pz}), 1100 (Pz ring breathing), 710 (β_{Pz}) cm^{-1}. $C_9H_{10}I_2N_4$ (428.01): calcd. C 25.26, H 2.35, N 13.09; found C 25.00, H 2.26, N 13.18.

1,3-Bis(4-iodo-3,5-dimethylpyrazol-1-yl)propane (5b): Yield: 0.522 g (83%) as colorless crystals. M.p. 93–94 °C (90% aq. EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 6 H, 3-Me-pz), 2.07 (quintet, J = 6 Hz, 2 H, $CH_2CH_2CH_2$), 2.38 (s, 6 H, 5-Me-pz), 3.55 (t, J = 6 Hz, 4 H, pz-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8 (5-Me-pz), 14.0 (3-Me-pz), 29.6 ($CH_2CH_2CH_2$), 46.6 (pz-CH_2), 62.7 (4-C-pz), 140.6 (5-C-pz), 149.3 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1510 (ν_{Pz}), 700 (β_{Pz}) cm^{-1}. $C_{13}H_{18}I_2N_4$ (484.12): calcd. C 32.25, H 3.75, N 11.57; found C 32.60, H 3.96, N 11.93.

Bis[2-(4-iodopyrazol-1-yl)ethyl] Ether (6a): Yield: 1.32 g (85%) as a colorless liquid. B.p. 190–191 °C (2 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.66 (t, J = 5 Hz, 4 H, OCH_2CH_2pz), 4.16 (t, J = 5 Hz, 4 H, OCH_2CH_2Pz), 7.30 (s, 2 H, 3-H-pz), 7.46 (s, 2 H, 5-H-pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4 (OCH_2CH_2pz), 69.5 (OCH_2CH_2pz), 70.5 (4-C-pz), 134.5 (5-C-pz), 144.6 (3-C-pz) ppm. IR (thin film): $\tilde{\nu}$ = 1500, 1430 (ν_{Pz}), 1090 (C–O), 1020 (Pz ring breathing), 720 (β_{Pz}) cm^{-1}. MS (EI): m/z (%) = 458 (3) [M]$^+$, 331 (3) [M – I]$^+$, 238 (100) [Pz$^{4-1}$CH$_2$CH$_2$OH]$^+$, 220 (85) [Pz$^{4-1}$CH=CH$_2$]$^+$, 205 (30) [M – 2I]$^+$, 194 (50) [Pz$^{4-1}$H]$^+$, 94 (50) [PzCH=CH$_2$]$^+$.

Bis[2-(4-iodo-3,5-dimethylpyrazol-1-yl)ethyl] Ether (6b): Yield: 0.757 g (74%) as colorless crystals. M.p. 126–127 °C (benzene). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 6 H, 3-Me-pz), 2.20 (s, 6 H, 5-CH_3-pz), 3.68 (t, J = 5.5 Hz, 4 H, OCH_2CH_2pz), 4.11 (t, J = 5.5 Hz, 4 H, OCH_2CH_2Pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (5-Me-pz), 14.1 (3-Me-pz), 49.8 (OCH_2CH_2pz), 62.5 (4-C-pz), 70.1 (OCH_2CH_2pz), 141.3 (5-C-pz), 149.6 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1510, 1420 (ν_{Pz}), 1100 (C–O), 1030 (Pz ring breathing) cm^{-1}. $C_{14}H_{20}I_2N_4O$ (514.14): calcd. C 32.70, H 3.92, N 10.90; found C 32.71, H 3.74, N 11.08.

Bis[2-(4-iodo-3,5-dimethylpyrazol-1-yl)ethyl]amine (7b): Yield: 0.696 g (58%) as colorless crystals. M.p. 70–71 °C (benzene). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 6 H, 3-Me-pz), 2.24 (s, 6 H, 5-CH_3-pz), 2.95 (t, J = 6 Hz, 4 H, NCH_2CH_2pz), 4.08 (t, J = 6 Hz, 4 H, NCH_2CH_2Pz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (5-Me-pz), 14.0 (3-Me-pz), 48.9 (NCH_2CH_2pz), 49.6 (NCH_2CH_2pz), 62.6 (4-C-pz), 140.6 (5-C-pz), 149.4 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1530, 1470 (ν_{Pz}), 1340 (βCH), 1040 (Pz ring breathing), 740 (β_{Pz}) cm^{-1}. $C_{14}H_{21}I_2N_5$ (513.16): calcd. C 32.77, H 4.12, N 13.65; found C 32.58, H 4.05, N 13.68.

1,4-Bis[2-(4-iodopyrazol-1-yl)ethyl]piperazine (8): Yield: 0.39 g (81%) as colorless crystals. M.p. 116–118 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 8 H, piperazine ring-CH_2), 2.78 (t, J = 6.5 Hz, 4 H, NCH_2CH_2pz), 4.22 (t, J = 6.5 Hz, 4 H, NCH_2CH_2Pz), 7.48 (s, 2 H, 3-H-pz), 7.51 (s, 2 H, 5-H-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1545 (ν_{Pz}), 1010 (Pz ring breathing), 765 (β_{Pz}) cm^{-1}. $C_{14}H_{20}I_2N_6$ (526.16): calcd. C 31.96, H 3.83, N 15.97; found C 31.62, H 3.80, N 15.81.

1,3-Bis(4-formyl-3,5-dimethylpyrazol-1-yl)propane (9b): Phosphorus trichloroxide (0.848 g, 5.5 mmol) was added dropwise over 5 min to an ice-chilled solution of compound **1b** (0.582 g, 2.50 mmol) in DMF (1 mL). The mixture was maintained at 100 °C until the completion of the reaction (5 h, TLC control), and then poured into water (30 mL). The solution was neutralized with aqueous NaOH and extracted with chloroform (5 × 20 mL). Combined organic extracts were dried with anhydrous Na_2SO_4, and the solvent was removed to yield dialdehyde **9b** as colorless crystals (0.66 g, 92%). M.p. 178–180 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (quintet, J = 6.5 Hz, 2 H, $CH_2CH_2CH_2$), 2.41 (s, 6 H, 3-Me-pz), 2.46 (s, 6 H, 5-Me-pz), 4.02 (t, J = 6.5 Hz, 4 H, pz-CH_2), 9.81 (s, 2 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.9 (5-Me-pz), 12.5 (3-Me-pz), 28.9 ($CH_2CH_2CH_2$), 45.3 (CH_2-pz), 118.1 (4-C-pz), 144.3 (5-C-pz), 151.2 (3-C-pz), 186.0 (CHO) ppm. IR (KBr): $\tilde{\nu}$ = 1650 (C=O), 1530, 1490 (ν_{Pz}), 1030 (Pz ring breathing), 780 (β_{Pz}) cm^{-1}. $C_{15}H_{20}N_4O_2$ (288.34): calcd. C 62.48, H 6.99, N 19.43; found C 62.79, H 7.10, N 19.43.

Bis[2-(4-formyl-3,5-dimethylpyrazol-1-yl)ethyl] Ether (10b): Dialdehyde **10b** was prepared similarly to product **9b** from compound **2b** (1.31 g, 5.0 mmol) and phosphorus trichloroxide (1.68 g, 11.0 mmol) in DMF (1.5 mL) as colorless crystals (1.29 g, 81%). M.p. 120–123 °C (benzene). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 6 H, 3-Me-pz), 2.36 (s, 6 H, 5-CH_3-pz), 3.71 (t, J = 5.5 Hz, 4 H, OCH_2CH_2pz), 4.02 (t, J = 5.5 Hz, 4 H, OCH_2CH_2Pz), 9.81 (s, 2 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.0 (5-Me-pz), 12.7 (3-Me-pz), 48.3 (O-CH_2CH_2-pz), 69.5 (O-CH_2CH_2-pz), 117.9 (4-C-pz), 145.1 (5-C-pz), 151.2 (3-C-pz), 185.5 (CHO) ppm. IR (KBr): $\tilde{\nu}$ = 1680 (C=O) 1540, 1400 (ν_{Pz}), 1100 (C–O), 1030 (Pz ring breathing), 780 (β_{Pz}) cm^{-1}. $C_{16}H_{22}N_4O_3$ (318.37): calcd. C 60.36, H 6.97, N 17.60; found C 60.05, H 6.63, N 17.40.

1,3-Bis(3,5-dimethylpyrazol-1-yl)propanedichlorozinc: A solution of ligand **2b** (0.116 g, 0.5 mmol) in diethyl ether (2 mL) was added to a solution of zinc chloride (0.068 g, 0.5 mmol) in the same solvent (6 mL). The immediately formed precipitate was filtered and dried in vacuo to give a colorless powder of the complex (0.134 g, 73%). M.p. 258–260 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 2.39 (s, 6 H, 3-Me-pz), 2.13 (br., 2 H, $CH_2CH_2CH_2$), 2.57 (s, 6 H, 5-Me-pz), 4.32 (br., 4 H, pz-CH_2), 4.17 (s, 2 H, 4-H-pz) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 12.0 (3-Me-pz), 14.0 (3-Me-pz), 31.2 ($CH_2CH_2CH_2$), 44.5 (pz-CH_2), 108.0 (4-C-pz), 143.3 (5-C-pz), 151.2 (3-C-pz) ppm. IR (KBr): $\tilde{\nu}$ = 1550, 1471 (ν_{Pz}), 1386 (βCH), 1048 (Pz ring breathing), 809 (β_{Pz}) cm^{-1}. $C_{13}H_{20}Cl_2N_4Zn$ (368.62): calcd. C 42.36, H 5.47, N 15.20; found C 42.15, H 5.37, N 15.58.

Bis[2-(3,5-dimethylpyrazol-1-yl)ethyl] Ether Dinitratocopper: A solution of ligand **2b** (0.524 g, 2 mmol) in acetone (5 mL) was added to a solution of copper(II) nitrate trihydrate (0.484 g, 2 mmol) in the same solvent (3 mL). The precipitated blue crystals were filtered after 24 h, washed with acetone, and dried in vacuo. Yield: 0.819 g (91%). M.p. 218 °C (dec.). IR (KBr): $\tilde{\nu}$ = 1555, 1430 (ν_{Pz}), 1482, 1290 (ν_3 mode of bidentate NO_3^-), 1385 (βCH), 1102 (C–O), 1019 (Pz ring breathing), 999 (ν_1 mode of NO_3^-), 802 (ν_2 mode of NO_3^-), 739, 710 (ν_4 mode of bidentate NO_3^-) cm^{-1}. $C_{14}H_{22}CuN_6O_7$ (449.91): calcd. C 37.37, H 4.93, N 18.68; found C 37.26, H 4.88, N 18.69.

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