NEW NITROGEN-RICH TRIPODAL MOLECULES BASED ON BIS(PYRAZOL-1-YLMETHYL)AMINES WITH SUBSTITUENTS MODULATING STERIC HINDRANCES AND ELECTRON DENSITY OF DONOR SITES

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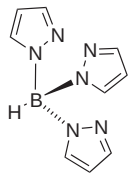
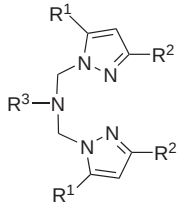
Eight new substituted bis(pyrazol-1-ylmethyl)amines have been prepared in one step condensation of 1-(hydroxymethyl)-3,5-disubstituted pyrazoles with a series of primary amines. The effect of substituents of divers bulkiness and electron donor/acceptor power that have been introduced to these tridentate molecules is visualised by ^{1}H NMR spectroscopy.
Keywords: Pyrazole; Tridentate ligands; Parallel synthesis; Symmetrical ligand.

The chemistry of nitrogen containing multipodal molecules is attracting current interest in life sciences due to their specificity for biological targets[1]. These compounds are also of importance for building polynuclear complexes[2] as models for bioinorganic systems[3–6] as well as for the discovery of new catalyst precursors[7]. The pyrazole ring seems to play a key role as it is involved in several types of chelating ligands[8]. Ligands containing several pyrazole rings were used in models that mimic active sites of copper proteins[9–11]. For instance, hydrotris(pyrazol-1-yl)borates **I** were studied as tripodal ligands in metal complexes, which has resulted in a discovery of new activation processes and new catalytic reactions[12–14].



I



II

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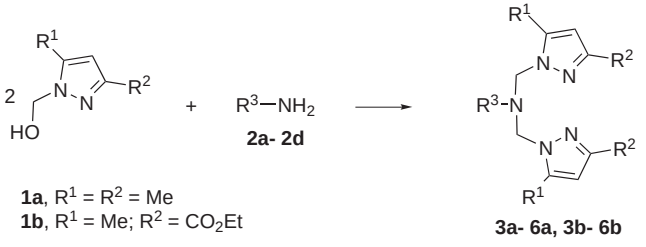
The bis(pyrazol-1-ylmethyl)amines **II** are of interest as potential six electron-donating ligands comprising two types of nitrogen donor groups as reported for metal-containing complexes with benzyl group for R^3 (lit.[15]). For instance, ligand **II** with $R^1 = R^2 = H$ and $R^3 = PhCH_2$ can coordinate to $CuCl_2$ via the central nitrogen atom and two nitrogen atoms, each from another pyrazole ring, thus acting as six-electron-donating ligands[15b]. Interestingly, the same ligand coordinates $ZnCl_2$ like a four electron-donating ligand via two nitrogen atoms of pyrazole rings[15b]. Furthemore, these compounds have been proved to show biological activity[16].

As the coordination behaviour of ligand **II** and the reactivity of the corresponding metal complexes can strongly depend on both the electron density on the nitrogen atoms and steric hindrances of substituents R^1, R^2 and R^3, it is of interest to increase the diversity of tridentate ligands **II**.

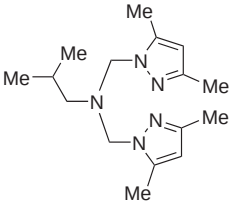
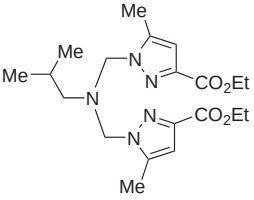
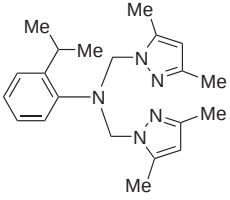
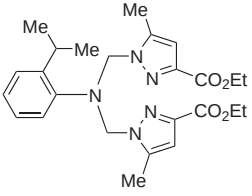
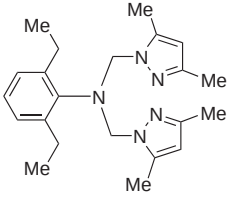
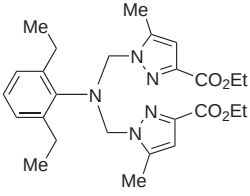
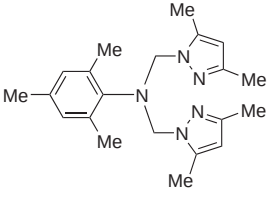
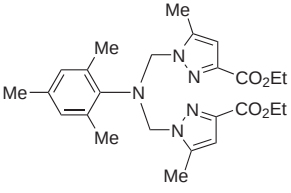
In this paper we report the synthesis of eight new bis(pyrazolyl)amines containing diverse bulky groups linked to the central nitrogen atom and various electron-acceptor substituents linked to pyrazole rings. In addition, we also report the modification of original synthesis procedure[15], which enables an automated parallel synthesis of bis(pyrazol-1-ylmethyl)amines by the condensation of an amine with 1-(hydroxymethyl)pyrazole derivatives (Scheme 1).



SCHEME 1

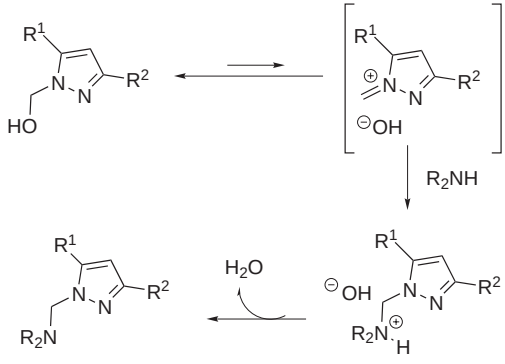
Coordination properties of the pyrazole-ring donor sites are sensitive to substituents linked to these rings. Therefore, we modified these properties of molecules **3**–**6** by introducing electron-donating Me and electron-withdrawing COOEt substituents to pyrazole rings, which was accomplished by using 1-(hydroxymethyl)-3,5-dimethylpyrazole (**1a**)[15c] and ethyl 1-(hydroxymethyl)-5-methyl-3-carboethoxypyrazole (**1b**)[16] as starting compounds. The nature of substituent R^3, particularly the electronic effect of alkyl versus aryl groups R^3, and the steric hindrance of R^3 could modify coordination properties of the central nitrogen donor site. Thus, four bulky amines **2**, i.e. isobutylamine and three different ring-substituted anilines (in ortho and para positions), were condensed with precursors **1a** and **1b**.

TABLE I
Structure and experimental yield of products **3**–**6**

Product		Yield, %	Product		Yield, %
3a		85	**3b**		85
4a		75	**4b**		75
5a		85	**5b**		82
6a		80	**6b**		80

These eight reactions were performed in a parallel way using an automated synthesiser[17]. The key point was to find an experimental protocol for the parallel purification process which is compatible with a diversity of properties (solubility, elution in preparative chromatography) of the eight different products. We have examined different approaches such as filtration on silica pad or liquid–liquid extraction. The best result was obtained by successive washings of crude products with diethyl ether and hexane. Analytical data indicated that this parallel purification process gives products of sufficient purity and can be used directly for our purposes. White solid products were stored at low temperature under nitrogen or used directly in order to avoid their degradation that is visualised by browning (particularly visible in the case R^3 = isobutyl).

Interestingly, although this type of reaction was previously reported, there is no clear description of its mechanism. A possible way could be based on equilibrium, between hydroxymethylpyrazoles and corresponding electrophilic iminium salts, displaced by nucleophilic attack of amines and followed by water elimination from formed ammonium salts (Scheme 2). Transformation of hydroxymethylamines into iminium salts was suggested by Petasis et al.[18] and the reaction of electrophilic iminium salts with various nucleophiles was also reported[19].



SCHEME 2

The impact of different groups R^1, R^2 and R^3 is visible on the chemical shift in ^{1}H NMR of the hydrogen atoms of pyrazolyl groups and of the two hydrogen atoms of the methylene bridges between the central nitrogen atom and the pyrazole rings. As expected, the hydrogen atoms of the pyrazole rings are more strongly influenced by the nature of R^1 and R^2 (5.69 ppm for **5a** and 6.47 ppm for **5b**) than by the nature of the R^3 group (5.69 ppm for **5a** and 5.78 ppm for **3a**). Protons of the methylene groups

are affected by both R^1, R^2 and R^3 as follows from the observed values for **5a** (5.33 ppm) and **3a** (4.85 ppm; the influence of R^3) and **3a** (4.85 ppm) versus **3b** (5.09 ppm; influence of R^1, R^2 groups).

The observed changes in chemical shifts of pyrazole-ring protons (from 5.69 to 6.37 ppm) and of methylene groups (from 4.85 to 5.55 ppm) prove that the introduction of various electron-acceptor and/or bulky substituents to pyrazole rings can be used for tuning the electron density on nitrogen atoms of these potential ligands. Besides, the introduction of COOEt substituent on pyrazole rings brings about potentially different coordination behaviour, as compared to that of already observed for similar ligands with R^1 and R^2 = H or Me [15], which is due to ability of CO group of the COOEt substituent to coordinate to metal atoms. Studies in this direction are in progress.

EXPERIMENTAL

All reactions were carried out in an inert atmosphere. Solvents were purified and dried under nitrogen by conventional methods. Analytical analyses were performed at CRMPO laboratories. High resolution mass spectrometer MS/MS ZABSpec TOF (Micromass) ESI mode was used. Elemental analyses were done using a Flash EA 1112 equipment. The ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50.33 MHz on a Bruker DPX 200 instrument. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra (wavenumbers in cm^{-1}) were measured on a Bruker IFS28 FT spectrometer. Compounds **1a** [15c] and **1b** [16] were prepared acoording to published methods. Amines **2** were purchased from Acros or Aldrich and used as supplied. The automated synthesis workstation ASW 1000 allows: liquid handling and dispensing, parallel synthesis in glass reactors (up to 122) with temperature control (–70 to +150 °C), reflux, inert atmosphere, work-up and purification by liquid–liquid extraction or parallel filtration and sequential washing, evaporation of solvents[20].

General Procedure of the Automated Synthesis (Chemspeed ASW 1000) of Bis(pyrazol-1-ylmethyl)amines

Stock solutions of derivatives **1** (1.66 mol/l) in CH_3CN and of amines **2** (0.83 mol/l) in CH_3CN were selectively dispatched into eight tubes to generate eight possible combinations (1.5 ml of **1** (2.5 mmol) and 1.5 ml of **2** (1.25 mmol)). After 4 h at 40 °C, the solutions were simultaneously transferred into eight tubes containing anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude products were washed with ether and hexane, and dried.

Compound **3a**: Yield 85%. IR (CH_2Cl_2): 3050, 2980 (–CH_3); 2830, 2700, 2520, 2450, 2350, 2200, 2100, 2050, 1660, 1550, 1480, 1450, 1370, 1270, 1150, 1100. ^{1}H NMR (200.132 MHz, $CDCl_3$): 5.78 (s, 2 H, -CH pyrazole ring); 4.85 (s, 4 H, -N-C**H**$_2$-N-); 2.25 (d, 2 H, -N-C**H**$_2$-CH-); 2.10 (s, 12 H, -CH_3); 1.55 (m, 1 H, $(CH_3)_2$-C**H**-CH_2-); 0.85 (d, 3 H, -CH_3); 0.65 (d, 3 H, -CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 147.68, 139.99, 106.07, 66.46, 57.12, 26.73, 20.73, 13.89, 11.29. HRMS (EI): calculated for $C_{13}H_{20}N_5$ $[M - C_3H_7]^+$ 246.17187; found: 246.1721.

Compound **4a**: Yield 75%. M.p. 68–70 °C. IR (CH_2Cl_2): 3054, 2986, 2830, 2685, 2521, 2410, 2305, 2155, 2121, 1967, 1886, 1655, 1551, 1506, 1421, 1271, 1192, 1153. ^{1}H NMR (200.132 MHz, $CDCl_3$): 7.15–6.90 (m, 3 H); 6.42 (d, 1 H); 5.65 (s, 2 H, -CH pyrazole ring); 5.35 (m, 4 H, -N-CH_2-N-); 3.45 (m, 1 H, -C**H**$(CH_3)_2$, *J* = 7.0); 2.22 (s, 6 H, -CH_3); 1.67 (s, 6 H, -CH_3); 0.99 (d, 6 H, (C**H**$_3)_2$-CH, *J* = 7.0). ^{13}C NMR (50 MHz, $CDCl_3$): 148.30, 142.67, 140.27, 127.36–124.59, 105.62, 67.38, 27.49, 23.78, 14.02, 11.10. HRMS (EI): calculated for $C_{16}H_{22}N_3$ [M – $C_5H_7N_2$]$^+$ 256.18137; found: 256.1815.

Compound **5a**: Yield 85%. M.p. 81–83 °C. IR (CH_2Cl_2): 3040, 2980, 2830, 2700, 2520, 2450, 2350, 1660, 1550, 1480, 1370, 1270. ^{1}H NMR (200.132 MHz, $CDCl_3$): 7.10–6.99 (m, 3 H, -CH benzene ring); 5.69 (s, 2 H, -CH pyrazole ring); 5.33 (s, 4 H, -N-CH_2-N-); 2.23 (s, 6 H, -CH_3); 2.10 (q, 4 H, -C**H**$_2$$CH_3$, *J* = 7.5); 1.6 (s, 6 H,-CH_3); 1.0 (t, 6 H, -CH_2C**H**$_3$, *J* = 7.5). ^{13}C NMR (50 MHz, $CDCl_3$): 131.86, 111.21, 71.55, 28.35, 20.2, 19.38, 16.15. For $C_{22}H_{31}N_5$ (365.3) calculated: 72.29% C, 8.55% H, 19.16% N; found: 72.45% C, 8.61% H, 19.22% N.

Compound **6a**: Yield 80%. M.p. 171–173 °C. IR (CH_2Cl_2): 3050, 2970, 2810, 2680, 2510, 2350, 2300, 2160, 2120, 2060, 1550, 1460, 1250, 1200, 1050. ^{1}H NMR (200.132 MHz, $CDCl_3$): 6.76 (s, 2 H, -CH benzene ring); 5.71 (s, 2 H, -CH pyrazole ring); 5.30 (s, 4 H, -N-CH_2-N-); 2.22 (s, 6 H, -CH_3 benzene ring); 2.20 (s, 3 H, -CH_3 benzene ring); 1.74 (s, 6 H, -CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 140.05, 137.62, 136.05, 129.83, 105.87, 65.54, 21.29, 17.84, 14.04, 10.75. For $C_{21}H_{29}N_5$ (351.5) calculated: 71.76% C, 8.20% H, 19.92% N; found: 71.10% C, 8.29% H, 19.69% N.

Compound **3b**: Yield 85%. IR (CH_2Cl_2): 3015, 2969, 2830, 2680, 2500, 2426, 2250, 2145, 2020, 1718 (–C=O); 1610, 1555, 1470, 1410, 1350, 1210, 1100, 1010, 980, 760. ^{1}H NMR (200.132 MHz, $CDCl_3$): 6.55 (s, 2 H, -CH pyrazole ring); 5.09 (s, 4 H, N-CH_2-N); 4.35 (q, 4 H, -OC**H**$_2$$CH_3$, *J* = 7.1); 2.35 (m, 2 H, -CH-C**H**$_2$-N-); 2.27 (s, 6 H, -CH_3); 1.65 (m, 1 H, -$(CH_3)_2$-CH-); 1.37 (t, 6 H, -OCH_2C**H**$_3$); 0.66 (d, 6 H, -CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 162.99, 143.05, 140.90, 109.21, 67.47, 61.24, 57.25, 26.65, 21.30, 14.79, 11.38. For $C_{20}H_{31}N_5O_4$ (405.5) calculated: 59.24% C, 7.71% H, 17.27% N; found: 59.28% C, 7.89% H, 17.31% N.

Compound **4b**: Yield 75%. M.p. 76–78 °C. IR (CH_2Cl_2): 3050, 2960, 2830, 2700, 2550, 2350, 2300, 1726 (–C=O); 1560, 1530, 1460, 1280, 1230, 1125, 980, 750. ^{1}H NMR (200.132 MHz, $CDCl_3$): 7.23–6.97 (m, 3 H, -CH benzene ring); 6.43 (s, 2 H, -CH pyrazole ring); 6.40 (m, 1 H, -CH benzene ring); 5.55 (m, 4 H, -N-CH_2-N-); 4.37 (q, 4 H, -OC**H**$_2$$CH_3$, *J* = 7); 3.35 (m, 1 H, -C**H**$(CH_3)_2$); 1.77 (s, 6 H, -CH_3); 1.38 (t, 6 H, -OCH_2C**H**$_3$, *J* = 7); 0.99 (d, 6 H, -CH_3, *J* = 6.9). ^{13}C NMR (50 MHz, $CDCl_3$): 163.10, 141.10, 128.04–127.42, 114.90, 108.66, 68.42, 61.27, 24.49, 14.82, 10.98. For $C_{25}H_{33}N_5O_4$ (467.6) calculated: 64.22% C, 7.11% H, 14.98% N; found: 64.62% C, 7.36% H, 14.57% N.

Compound **5b**: Yield 82%. M.p. 123–125 °C. IR (CH_2Cl_2): 3035, 2966, 2830, 2520, 2450, 2300, 2245, 2150, 2050, 1980, 1725 (–C=O); 1608, 1555, 1490, 1410, 1385, 1250, 1210, 1180, 1160, 1110. ^{1}H NMR (200.132 MHz, $CDCl_3$): 7.20–7.00 (m, 3 H, -CH benzene ring); 6.47 (s, 2 H, -CH pyrazole ring); 5.49 (s, 4 H, -N-CH_2-N-); 4.37 (q, 4 H, -OC**H**$_2$$CH_3$, *J* = 7.1); 2.08 (q, 4 H, -C**H**$_2$$CH_3$, *J* = 7.5); 1.78 (s, 6 H, -CH_3); 1.39 (t, 6 H, -OCH_2C**H**$_3$, *J* = 7.1); 1.02 (t, 6 H, -CH_2C**H**$_3$, *J* = 7.5).^{13}C NMR (50 MHz, $CDCl_3$): 163.24, 144.01, 143.26, 142.01, 140.35, 128.01, 126.95, 108.91, 67.27, 61.21, 23.08, 15.01, 10.89.

Compound **6b**: Yield 80%. M.p. 151–153 °C. IR (CH_2Cl_2): 3030, 2960, 2831, 2685, 2521, 2430, 2305, 2254, 2155, 2054, 1996, 1714 (–C=O); 1604, 1551, 1488, 1421, 1388, 1258, 1220, 1181, 1155, 1108. ^{1}H NMR (200.132 MHz, $CDCl_3$): 6.77 (s, 2 H, -CH benzene ring); 6.47 (s, 2 H, -CH pyrazole ring); 5.46 (s, 4 H, -N-CH_2-N-); 4.36 (q, 4 H, -OC**H**$_2$$CH_3$, *J* = 7.1);

2.20 (s, 3 H, -CH_3); 1.79 (s, 6 H, -CH_3); 1.71 (s, 6 H, -CH_3); 1.37 (t, 6 H, -$OCH_2C\mathbf{H}_3$, J = 7.1). ^{13}C NMR (50 MHz, $CDCl_3$): 163.21, 143.124, 140.41, 137.30, 137.10, 130.09, 108.88, 66.77, 61.17, 21.28, 17.82, 14.78, 10.81. For $C_{25}H_{33}N_5O_4$ (467.6) calculated: 64.22% C, 7.11% H, 14.98% N; found: 64.31% C, 7.39% H, 14.96% N.

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