New functionalised C,C-pyridylpyrazoles: synthesis and cation binding properties

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The synthesis of two new C,C-pyridylpyrazole isomers with a functionalised arm is described. The complexation capabilities of these ligands compared to their homologues towards bivalent metals (Hg^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}) and alkali metal ions (K^+, Na^+, Li^+) were investigated using a liquid–liquid extraction process. The percentage limits of extraction were determined by atomic absorption measurements.

Keywords: C,C-pyridylpyrazole, liquid–liquid extraction, cations, atomic absorption

Chelating ligands based on the pyrazole ring have been described extensively in the literature[1-6] including several reviews.[7-9] In our recent work, a series of acyclic pyrazole compounds containing one, two, three or four pyrazole rings were prepared and demonstrated to extract only transition metal cations,[10-15] whereas macrocyclic pyrazolic compounds are expected to also form stable complexes with alkali metals.[16-18] This aptitude is mainly due to the presence of sp^2 hybrid nitrogen donors with the involvement of geometry and the nature of the ligands.

Pyrazole-associated pyridine groups showed also the ability to complex transition metal ions.[19-24] However, complexation studies of pyridylpyrazole compounds are less well-known in the literature. It was therefore interesting to increase the diversity of pyridylpyrazole-based ligands with a view to study their complexation capabilities compared to ligands with pyrazoles units only.

Here, we report the synthesis of two new C,C-pyridylpyrazole isomers **5** and **6** (Fig. 1) with a donor heteroatom in a side chain. The complexation capabilities of these new functionalised C,C-pyridylpyrazole isomers **5** and **6** compared to their homologues such as unfunctionalised C,C-pyridylpyrazole 7,[23] C,N-pyridylpyrazole 8[24] and pyrazolylpyrazole 9[11] ligands were investigated using a liquid–liquid extraction process towards bivalent metal ions (Hg^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}) and alkaline metal ions (Li^+, Na^+, K^+). The relative capabilities of theses receptors in extracting theses cations were determined by the measurement of extracted cation percentage by atomic absorption.

Results and discussion

The preparation of the desired ligands **5** and **6** was carried out in two ways and the strategy is given below (Scheme 1). The first way includes only one step and involves condensation of the diketone **1**[25] with 2-hydroxyethylhydrazine using the same method as described in the literature for the synthesis of N-(2-hydroxyethyl)-3,5-dimethylpyrazole.[26] Under this method, the β-isomer **6** and the α-isomer **5** were obtained after separation and purification on silica gel chromatography, in 54 and 2% yields respectively. Theses structures were identified on the basis of their spectroscopic data.

In order to direct the reaction towards the dominating formation of the desired α-isomer **5**, we tried another way of synthesis. According to this method, the α-isomer **5** was prepared in three steps from the diketone **1**.[25] Action of hydrazine monohydrate on diketone **1** leads to the formation of pyridylpyrazole **2** in a 70% yield.[23] Alkylation of compound **2** with ethylbromoacetate in THF was carried out under solid-liquid phase transfer catalysis to favour the α-isomer.[27] Thus, one isolated major product **3** as the α-isomer was formed in 20% yield. The second positional isomer **4** was also isolated but with a very low yield (1%).

The poor yield of this reaction (20%) can be possibly due to the more conjugated nature of 3-(2-pyridyl)pyrazole which delocalises the negative charge when it is deprotonated, making it a poorer nucleophile. This poor yield was not surprising as bis[3-(2-pyridyl)pyrazol-1-yl]methane[28] was already reported under the same procedure in only a 14% yield. Compound **3** was then converted in the presence of $LiAlH_4$ to give a 70% yield of the corresponding alcohol **5**.

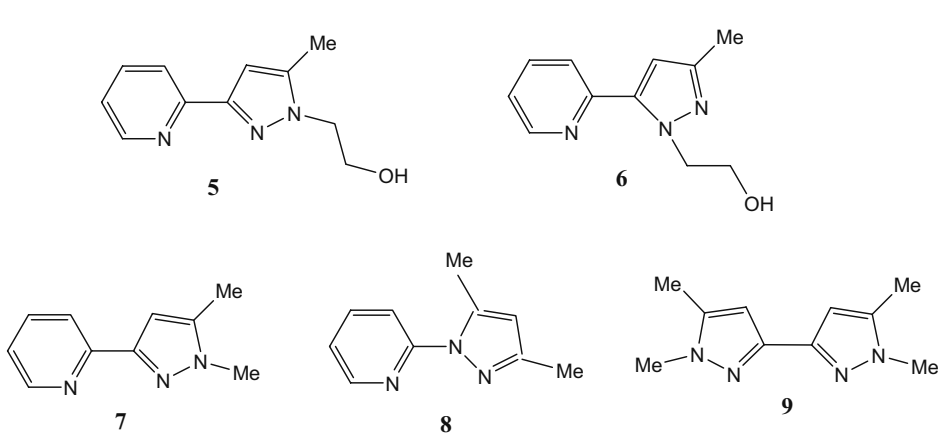

Fig. 1 Structures of synthesised C,C-pyridylpyrazole isomers **5** and **6** and literature ligands **7**,[23] **8**[24] and **9**.[11]

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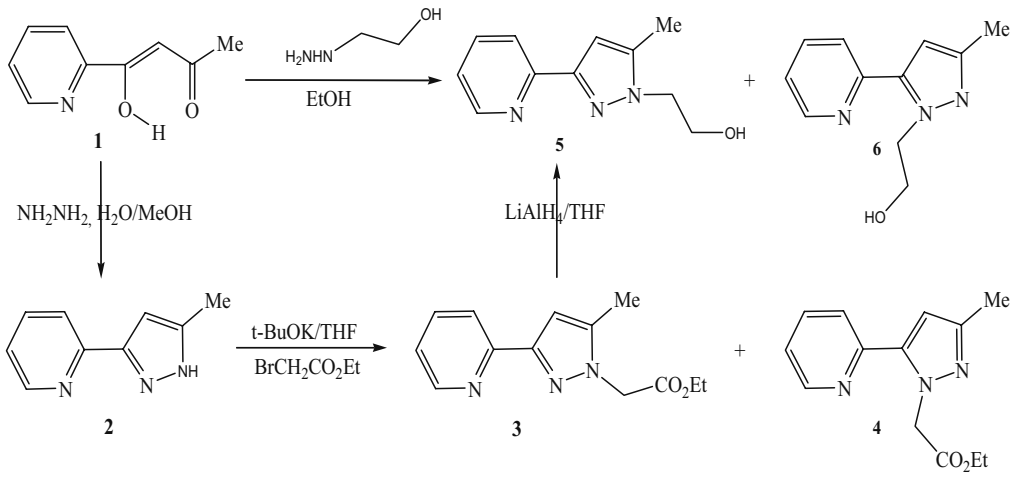

Scheme 1

Liquid–liquid extraction of individual cations

We used this method in order to determine, and thereafter to compare, the relative complexing capabilities of these pyridylpyrazole derivatives **5–9** towards bivalent and alkali metal ions (Hg^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}, Li^{+}, Na^{+} and K^{+}). Metal nitrates were extracted into the organic phase by complex formation with the pyridylpyrazole receptors. The percentage limits of extraction were determined by atomic absorption and the results are given in Table 1.

Results in Table 1 show that in analogy to our previous work[10-18] in which acyclic pyrazoles extract only the bivalent metal cations when the macrocyclic pyrazolic compounds are expected to form stable complexes both with bivalent and alkali metals, we demonstrate also here an affinity of these new acyclic ligands (type sp^2 nitrogen only) with the bivalent metal cations, with no complexation being observed toward alkali cations.

The strong ability of nitrogen to complex mercury was demonstrated for our previous ligands.[10-18] However, the present ligands **5–7** have a very weak affinity towards this metal.

We notice for these types of ligands a modest affinity only towards copper and lead with a very weak or a zero affinity towards others metals. We can thus suggest an important selectivity for these ligands towards copper and lead.

Contrary to the literature, in which a donor atom in a side chain of lariat ethers increases the binding ability of the macrocycle,[29-31] the comparison between **5** or **6** with a donor atom in a side chain and **7** without a donor atom shows that there is little change in the percentage of complexation. Indeed, we can conclude here that the complexation was due to the ligand nitrogens without contribution of a side arm. Moreover compound **3** acts in a similar way to compounds **5** and **7**. This confirms the above-mentioned assumption.

The spacing of this contribution makes the *chelating* effect responsible for the complexation ability. Indeed, when the geometry supports this effect, a stable complex is formed. In most cases, the bipyrazole groups and similar derivatives act as *convergent* chelating bidentate donors. The term *convergent* refers to the nitrogen donor atoms coordinating to the same metal centre leading to a five-membered ring which is thus part of several such rings when the whole ligand is considered. It is well known[32] that five-membered ring chelates are more stable than six-membered and four-membered ones.

We notice that the structure with a C-N junction, pyridylpyrazole **8**, rather than a C–C junction, pyridylpyrazole **7**, has stronger binding properties especially for mercury because of greater flexibility, allowing the donor site to adopt the best binding position.

Moreover, we noticed a double affinity for C,C-pyrazolylpyrazole ligand **9** (type sp^2 pyrazole) compared to its homologue pyridylpyrazole **8** (type sp^2 pyridine), we can thus emphasise the novel complexation properties of the ligands containing linked pyrazole groups compared to the pyridinic groups. Consequently, the affinity toward mercury follows the following order: C,C-bipyrazole (65%) > C,N-pyridylpyrazole (32%) > C,C-pyridylpyrazole (4%).

Conclusion

In conclusion, new acyclic C,C-pyridylpyrazole-based ligands were prepared and only form complexes with bivalent metal cations. They do not complex alkali metal cations at all. A modest affinity was observed towards copper and lead. However, ligands with pyrazole-type sp^2 nitrogen are the most effective.

Experimental

All solvents and other chemicals, obtained from usual commercial sources, were of analytical grade and used without further purification. The NMR spectra were obtained with a Bruker AC 300 spectrometer. Elemental analyses were performed by Microanalysis Central Service (CNRS). Molecular weights were determined on a JEOL JMS DX-300 Mass Spectrometer. Atomic absorption measurements were performed by Spectra Varian A.A. 400 Spectrophotometer.

Synthesis of **3** *and* **4**: A mixture of **2** (3 g; 18.87×10^{-3} mol) and potassium tert-butoxide (2.22 g; 19.82×10^{-3} mol) in anhydrous THF

Table 1 Yields of extraction of various studying metals by ligands **5–9**

	Hg^{2+}	Cd^{2+}	Pb^{2+}	Cu^{2+}	Zn^{2+}	Li^{+}	Na^{+}	K^{+}
5	9	0	7	15	0	0	0	0
6	4	3	12	13	0	0	0	0
7	4	3	10	20	0	0	0	0
8	32	1	13	9	0	0	0	0
9[11]	65	9	27	17	6	0	0	0

(60 mL) was refluxed for 2 h. After cooling to 0 °C, a solution of ethylbromoacetate (3.85 g; 23.05 × 10^{-3} mol) in THF (20 mL) was slowly added. The reaction mixture was stirred for one night at room temperature then filtered and the solvent was evaporated to dryness. The obtained residue was purified on silica using the mixture (10% ethylacetate/90% hexane) as eluant to give a 20% yield of **3** as a white solid and 1% yield of **4** (yellow oil).

3: White solid. M.p. = 58–60 °C (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.26 (t, $J_{H,H}$ = 7.17 Hz, 3 H, CH_2–CH_3), 2.29 (s, 3 H, –CH_3), 4.22 (q, $J_{H,H}$ = 7.17 Hz, 2 H, –CH_2–CH_3), 4.90 (s, 2 H, N–CH_2–), 6.71 (s, 1 H, Pz-H), 7.17 (m, 1 H, Py-H_β), 7.69 (m, 1 H, Py-H_γ), 7.85 (m, 1 H, Py-H_δ), 8.60 (m, 1 H, Py-H_α) ppm; ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 11.20 (CH_3), 14.14 (–CH_3), 51.06 (N–CH_2–), 61.89 (O–CH_2–), 104.81 (Pz C–H), 120.16 (Py C–H_δ), 122.41 (Py C–H_β), 136.76 (Py C–H_γ), 141.01 (Pz CCH_3), 149.12 (Py C–H_α), 150.40 (Py C), 167.68 (C=O) ppm; Anal. Calcd for $C_{13}H_{15}N_3O_2$: C 63.66, H 6.16, N 17.13. Found: C 63.60, H 6.15, N 17.22%; *m/z* 245 ($M^{+\cdot}$). IR (KBr): ν(C=O) = 1740 cm^{-1}.

4: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17 (t, $J_{H,H}$ = 7.17 Hz, 3 H, CH_2–CH_3), 2.23 (s, 3 H, –CH_3), 4.13 (q, $J_{H,H}$ = 7 Hz, 2 H, –CH_2–CH_3); 5.4 (s, 2 H, N–CH_2–), 6.47 (s, 1 H, Pz-H), 7.20 (m, 1 H, Py-H_β), 7.69 (m, 2 H, Py-H$_{\gamma,\delta}$), 8.65 (d, 1 H, Py-H_α) ppm; Anal. Calcd for $C_{13}H_{15}N_3O_2$: C 63.66, H 6.16, N 17.13. Found: C 63.57, H 6.12, N 17.25%; *m/z* 245 ($M^{+\cdot}$). IR (KBr): ν(C=O) = 1760 cm^{-1}.

(5): To a solution of $LiAlH_4$ (450 mg; 11.84 × 10^{-3} mol) in anhydrous diethyl ether (20 mL), cooled at 0 °C, was slowly added pyridylpyrazole **3** (1.15 g; 4.69 × 10^{-3} mol) in anhydrous diethyl ether (20 mL). The mixture was stirred under reflux for 2 h. After cooling, water (0.45 mL), aqueous sodium hydroxide (15%, 0.45 mL) and then water (1.35 mL) were added successively to the mixture at 0 °C. The solid material was filtered and the residue was washed with hot THF. The filtrate and THF washings were concentrated under reduced pressure to give a 70% yield of **5** as a white solid. M.p. = 50–52 °C (CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.33 (s, 3 H, CH_3), 4.09 (t, $J_{H,H}$ = 4.32 Hz and 4.71, 2 H, N–CH_2), 4.19 (t, $J_{H,H}$ = 4.32 Hz and 4.71, 2 H, –CH_2OH), 6.68 (s, 1 H, pz-H), 7.21 (t, 1 H, H_β), 7.73 (m, 1 H, H_γ), 7.88 (d, 1 H, H_δ), 8.60 (d, 1 H, H_α) ppm; ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 11.24 (CH_3), 50.45 (N–CH_2), 61.59 (–CH_2–OH), 104.12 (PzC-H), 120.05 (PyC-H_δ), 122.44 (PyC-H_β), 136.83 (PyC-H_γ), 140.64 (CCH_3), 149.10 (PyC-H_α), 149.10 (PzC), 150.37 (PyC) ppm; Anal. Calcd for $C_{11}H_{13}N_3O$: C 65.02, H 6.40, N 20.69. Found: C 64.90, H 6.39, N 20.71%; *m/z* 203 ($M^{+\cdot}$). IR (KBr): ν(OH) = 3200 cm^{-1}.

6: To a solution of 1-pyridin-2-yl-butane-1,3-dione **1** (1.5 g; 9.2 × 10^{-3} mol) in absolute ethanol (50 mL) at 0 °C, was slowly added a solution of 2-hydroxyethylhydrazine (0.7 g; 9.2 × 10^{-3} mol) in absolute ethanol (10 mL). The mixture was stirred at room temperature for 2 h. Then, the solvent was removed under reduced pressure and the obtained residue was purified on silica gel using (20% ethanol/80% ether) to give 54% yield of **6** as a brown solid and 2% yield of **5** as a white solid. The solid **6** was recrystallised using methanol to give colourless crystals of **6**. M.p. = 90–93 °C (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.34 (s, 3 H, CH_3), 4.12 (t, $J_{H,H}$ = 4.86 Hz and 5.40 Hz, 2 H, –CH_2OH), 4.59 (t, $J_{H,H}$ = 4.86 Hz and 5.40 Hz, 2 H, N–CH_2–), 6.37 (s, 1 H, pz-H), 7.32 (m, 1 H, H_β), 7.60 (d, 1 H, H_δ), 7.82 (t, 1 H, H_γ), 8.62 (d, 1 H, H_α) ppm; ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 13.48 (–CH_3), 52.29 (N–CH_2–), 62.91 (–CH_2–OH), 106.37 (Pz C–H), 122.94 (Py C–H_β), 123.62 (Py C–H_δ), 137.73 (Py C–H_γ), 142.22 (Pz C), 148.05 (Pz CCH_3), 148.31 (Py C–H_α), 148.95 (Py C) ppm. Anal. Calcd for $C_{11}H_{13}N_3O$: C 65.02, H 6.40, N 20.69. Found: C 65.00, H 6.39, N 20.74%; *m/z* 203 ($M^{+\cdot}$). IR (KBr): ν(OH) = 3260 cm^{-1}.

Extraction experiments: A solution of 7 × 10-5 M of every pyridylpyrazole in CH_2Cl_2 (25 mL) was stirred for 2 h with an aqueous solution (25 mL) of metal nitrates 7 × 10^{-5} M; the complexation was followed by measuring the concentration of cations in the aqueous phase by atomic absorption. The temperature remained constant during all the experiments at 25 °C and at pH 7 measured by a pH-meter.

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