

Pyrazole derivatives with *N*-pivot functionalized donor-group. Synthesis and preliminary metals binding properties.

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Abstract- The synthesis of pyrazoles ligands with *N*-pivot side-arm bearing a functionalized donor-group is reported. Complexation capabilities of these ligands towards bivalent metals (Hg^{2+} , Cd^{2+} , Pb^{2+} , Cu^{2+} , Zn^{2+}) and alkali metal ions (K^+ , Na^+ , Li^+) were investigated using liquid-liquid extraction process and compared to the *C*-pivot pyrazole one. The percentage limits of extraction were determined by atomic absorption measurements.

Keywords: Pyrazoles; Liquid-liquid extraction; Cations; Atomic absorption.

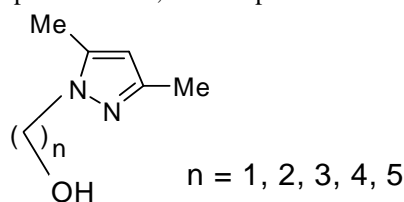
1. Introduction

Pyrazoles represent a class of compounds endowed with a great interest in recent years. These receptors are well known for their ability to form stable complexes with alkali cations [1-5] and transition metals [6-9]. This is evident from the large number of articles, several of them being reviews [10-12].

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 bivalent metal cations [13-16] whereas macrocyclic pyrazolic compounds are expected to form stable complexes both with bivalent and alkali metals [17,18]. This aptitude is mainly owed to the presence of sp^2 hybrid nitrogen donors with the involvement of geometry and nature of ligands.

On the other hand, it is necessary to consider the great effect of side arms in coordination chemistry. Indeed, it has been found that a donor atom in a side chain of lariet ethers increases the binding ability of the macrocycle [19-21].

In this context we synthesized some pyrazolic structures (Figure 1) with donor-oxygen in a side chain in order to investigate the effect of the donor group on the chelating properties of the pyrazole derivatives towards bivalent metal ions (Hg^{2+} , Cd^{2+} , Pb^{2+} , Cu^{2+} , Zn^{2+}) and alkaline metal ions (Li^+ , Na^+ , K^+) using liquid-liquid extraction process. The relative capacities of these receptors in extracting these cations were determined by the measurement of extracted cation percentage by atomic absorption. Indeed, the compounds below are developed:



Hg^{2+} , Cd^{2+} , Pb^{2+} , Cu^{2+} , Zn^{2+} , Li^+ , Na^+ , K^+

Fig. 1. Compounds and cations studied.

2. Experimental

2.1. Apparatus

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.

2.2. Synthesis of: 1-(3-Hydroxypropyl)-3,5-dimethyl-1H-pyrazole **5** and 1-(4-Hydroxybutyl)-3,5-dimethyl-1H-pyrazole **6**:

Compounds **5** and **6** were prepared according to the our recent reference [22].

2.3. Synthesis of 1-(5-Hydroxypentyl)-3,5-dimethyl-1H-pyrazole **7**:

A mixture of 3,5-dimethylpyrazole **1** (4.1×10^{-2} mol) and potassium tert-butoxide (4.1×10^{-2} mol) in 150 ml of THF was stirred under reflux for 30 min. Synthon bromide (4.1×10^{-2} mol) in 100 ml of THF was then added slowly. After stirring under reflux for 6 h, the mixture was filtered, evaporated and the residue was separated on silica gel using CH_2Cl_2 as eluant to give the target compound. Yield: 70 %; ^1H NMR (CDCl_3): δ (ppm): 1.20-1.79 (m, 6H, $\text{NCH}_2(\text{CH}_2)_3\text{CH}_2\text{OH}$); 2.19 (s, 1H, OH); 2.33 (s, 6H, 2 CH_3); 3.60 (m, 2H, CH_2OH); 3.88 (m, 2H, CH_2N); 5.85 (s, 1H, H-Pz); ^{13}C NMR (CDCl_3): δ (ppm): 11.8 (CH_3); 13.1 (CH_3); 15.3 ($-\text{CH}_2-$); 24.5 (N- CH_2-CH_2); 28.5 ($-\text{CH}_2-\text{CH}_2-\text{OH}$); 49.1 (N- CH_2-); 60.4 ($-\text{CH}_2-\text{OH}$); 104.6 (Pz $\text{C}-\text{H}$); 139.4 (Pz $\text{C}-\text{CH}_3$); 147.4 (Pz $\text{C}-\text{CH}_3$); Anal. calcd for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}$: C 65.90, H 9.95, N 15.37. Found: C 65.97, H 9.80, N 15.42; m/z : 183 $[\text{M}+1]^+$ (FAB>0).

2.4. Extraction experiments:

A solution of 7×10^{-5} M of pyrazolic group in CH_2Cl_2 (50 ml) was stirred for 2 h with an aqueous solution (50 ml) of metal nitrates (7×10^{-5} M); the complexation was followed by measuring the concentration of cations in an aqueous solution by atomic absorption. The temperature remained constant during all the experiments at 25°C and at pH 7.

3. Results and discussion

3.1. Synthesis links

Compound **2** was already reported by several old and recent works [23-26]. Compound **3** was reported in our recent work in another method [27]. Compounds **5** and **6** were synthesised according to our recent work [22]. The result of our investigation was given below (Scheme 1): For 1-hydroxymethyl-3,5-dimethylpyrazole **2**: Many heterocycles with a ring NH group react with formaldehyde to yield addition products of type $\text{N}(\text{CH}_2\text{OH})$. Indeed, a variety of C-substituted N-unsubstituted pyrazole react with formaldehyde to give the corresponding N-hydroxymethyl derivatives, including 3,5-dimethylpyrazole. The synthesis of 1-(2-hydroxyethyl)-3,5-dimethylpyrazole **3** was carried out in three way. The first way consists in the direct alkylation of 3,5-dimethylpyrazole **1** with 2-bromoethanol in the presence of t-BuOK as base leading to product **3** in a 62% yield. The second way consists in the alkylation of 3,5-dimethylpyrazole **1** with ethyl bromoacetate in the presence of t-BuOK as base leading to product **4** in a 34% yield, followed by its conversion to product **3** in a 90% yield using LiAlH_4 as reducing agent. In the last way, the target product **3** was carried out in one step, as described in our previous works [27, 28], by condensation of pentan-2,4-dione with 2-hydroxyethylhydrazine in ethanol as solvent to give 78% yield. A new compound **7** was obtained in a 70% yield, by the alkylation of 3,5-dimethylpyrazole **1** with 5-bromopentanol in the presence of t-BuOK as base.

In order to show a possible contribution of donor oxygen in a side chain on the cation binding, we prepared other similar pyrazole compound, 1,3,5-trimethylpyrazole **8**, (Figure 2) without donor atom in a side arm. This known compound **8** was obtained in a 73 % yield by alkylation of **1** with methyl iodide in the presence of t-BuOK as base. The comparison was also checked using the 3-(hydroxymethyl)-1,5-dimethylpyrazole **9** [14] with C-pivot functionalized donor-group (Figure 2).

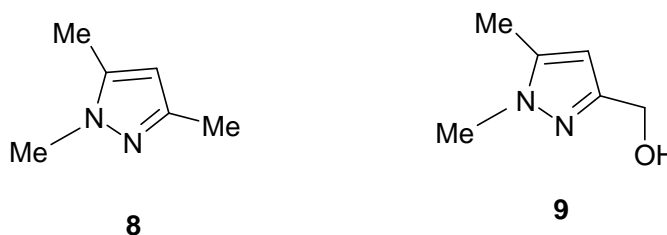
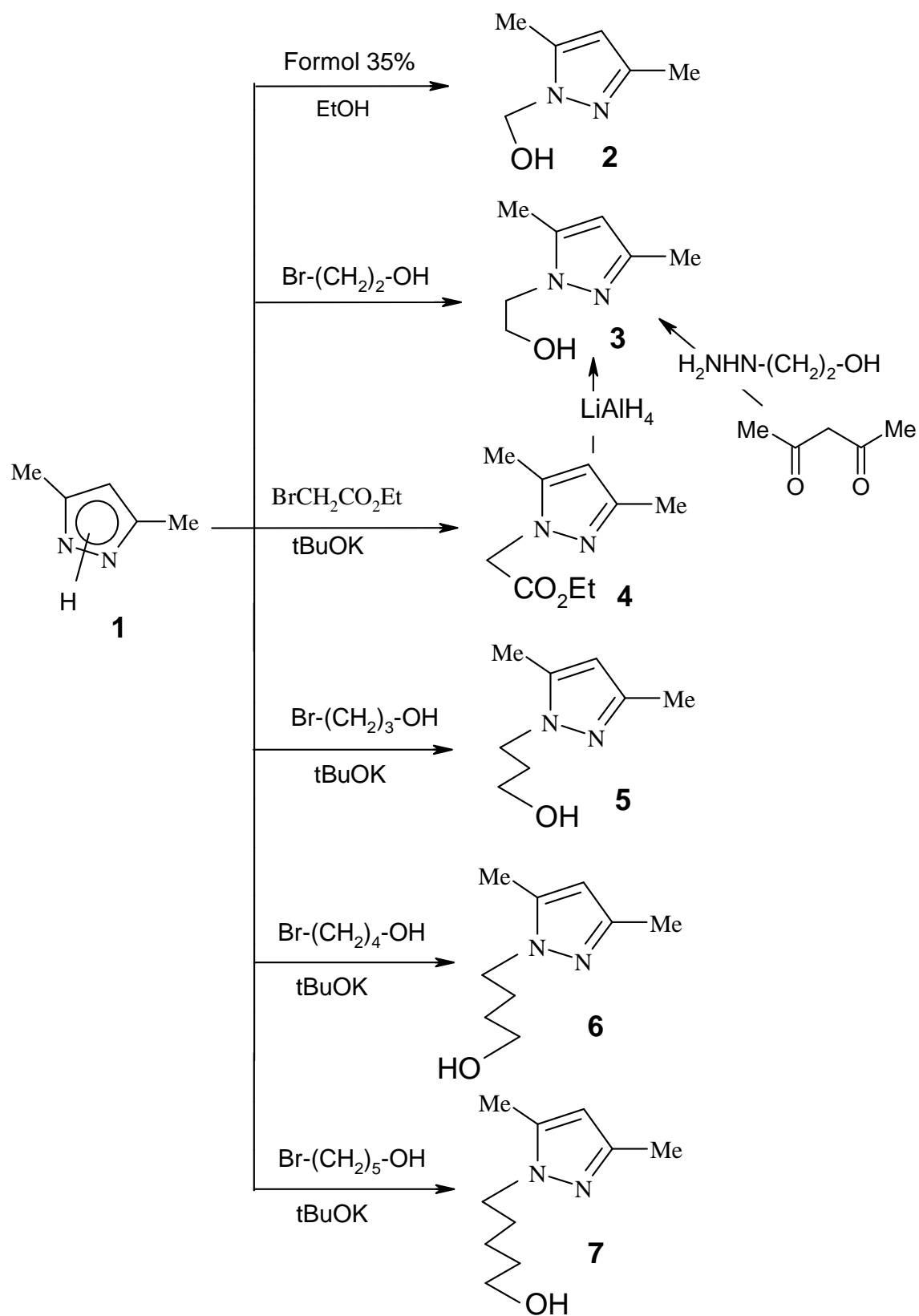


Fig. 2. Molecular structure of compounds **8** and **9**.



Scheme 1. General pathway for preparing pyrazolic compounds

3.2. Liquid-liquid extraction of individual cations

In order to compare the relative capabilities of ligands **2-9** in extracting Hg^{2+} , Cd^{2+} , Pb^{2+} , Cu^{2+} , Zn^{2+} , Li^+ , Na^+ and K^+ cations we used liquid-liquid extraction of individual cations. Metal nitrates were extracted into the organic layer by complex formation with pyrazolic receptors. The percentage limits of extraction were determined by atomic absorption. The results are given in table 1.

Results in Table 1 show that in analogy to our previous work [13-18] 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 pyrazoles only with the bivalent metal cations, with no complexation being observed toward alkali cations.

Table 1. Yields of extraction of various studing metals by pyrazolic ligands **2-9**.

Ligand	Hg^{2+}	Cd^{2+}	Pb^{2+}	Cu^{2+}	Zn^{2+}	Li^+	Na^+	K^+
2	65	17	26	18	7	0	0	0
3	50	6	8	12	0	0	0	0
5	50	5	3	7	0	0	0	0
6	70	15	25	19	5	0	0	0
7	70	18	28	20	4	0	0	0
8	11	3	3	7	0	0	0	0
9 ¹⁴	13	6	0	-	-	0	0	0

The affinity of these hosts is especially high for mercury. This is not surprising if the high donor properties of nitrogen towards this metal are considered. Also, the strong ability of nitrogen to complex mercury was demonstrated for our previous ligands [13-18].

While comparing **2**, **3** and **5**, we notice that compound **2** presents higher chelating properties. Indeed compound **2** forms a five-membered ring which is thus part of several such rings when the whole ligand is considered, while compounds **3** and **5** leads to a six- and seven-membered ring respectively with the complexated metal cation. It is well known [29] that five-membered ring chelates are more stable than six-membered one and others.

However, we notice a definitely high percentage of complexation of **6** and **7** with a longer side chain. This is due probably to the influence of the donor-oxygen supported by the length of the side chain on the complexation which acts as an "intermolecular" entity.

The comparison between **2-7** with a donor atom in a side chain and **8** without a donor atom shows a remarkable change in the percentage of complexation. Indeed, we can conclude here that the complexation was due to the ligand nitrogens with contribution of a side arm. This is not surprising since the fragment N-(2-hydroxyethyl)-3,5-dimethylpyrazole acts as a bidentate N,O ligand in coordination compounds with some transition metal ions [30].

On the other hand, it is known that a donor atom in a side chain of lariat ethers increases the binding ability of the macrocycle [19-21]. Furthermore, structures with side arms attached at nitrogen (N-pivot lariat ethers) instead of a carbon (C-pivot lariat ethers) have stronger binding properties because of greater flexibility, allowing the donor site to have the best binding position [31]. To check this rule, we compared compound **2** with N-pivot side arm and which leads to stable five-membered ring chelate with the similar structure 3-(hydroxymethyl)-1,5-dimethylpyrazole **9** [14]. This last ligand leads also to stable five-membered ring chelate, but has a same C-pivot side arm. In analogy to the literature [31], the results show that structure **2** with side arm attached at nitrogen instead of a carbon (structure **9**) has stronger binding properties.

4. Conclusion

In conclusion, metal cations and macrocyclic pyrazolic compounds are expected to form stable complexes both with bivalent and alkali metals, while the acyclic pyrazole ligands reported here only form complexes with bivalent metal cations, especially with mercury. The affinity was higher for structures with side arms (i) attached at nitrogen instead of a carbon, (ii) leading to stable five-membered ring chelate or (iii) with sufficient length allowing the donor-atom to act as an "intermolecular" entity.

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