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New generation of tetrapyrazolic macrocycles: Synthesis and examination of their complexation properties and antibacterial activity

Tarik Harit [a], Reda Bellaouchi [b], Chakib Mokhtari [a], Brahim El Bali [a], Abdeslam Asehraou [b], Fouad Malek [a, *]

[a] Laboratory of Organic, Macromolecular Chemistry and Natural Products -URAC 25- Faculty of Sciences, Mohamed 1st University, Bd Mohamed VI, BP: 717, Oujda 60000, Morocco
[b] Laboratory of Biochemistry and Biotechnology, Faculty of Sciences, Mohammed First University, BP 717, Oujda, 60000, Morocco

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ABSTRACT

The synthesis of three macrocycles, containing four pyrazolic units, with different side arms is described and the crystal structure of one of the intermediate compounds is also presented. The complexing properties of these compounds towards alkaline metal ions (Cs^+, K^+, Na^+ and Li^+) was studied by the liquid–liquid extraction process. The percentage values of extraction were determined by atomic absorption measurements and UV spectroscopy. These macrocycles extract selectively K^+ and highlight the good effect of using a long side chain bearing a donor group, on the percentage of extraction of the alkali cations K^+, Na^+ and Li^+. They also showed a good antibacterial against Gram-positive and Gram-negative microorganisms with minimum inhibitory concentrations at the range of 32–64 μg/mL.

1. Introduction

Organic macrocycles with 1H-pyrazole units have taken much more of interest in the past years due to coordination properties of this small heterocycle.[1–4] They are characterized by a central hydrophilic cavity in which, depending on its diameter, metal cations are selectively bound. Over the last decade, several tetrapyrazolic macrocycles have been synthesized. They can extract both alkali and transition metal cations,[5–7] in contrast to acyclic pyrazolic ligands which can extract only transition metal cations.[8–13] Furthermore, it was found that the ionophore properties of such compounds were considerably influenced by several factors such as the size and geometry of the macrocyclic cavity and the presence of a donor atom in a side arm.[6,14] In fact, it was reported that compounds with N-pivot lariat ethers possess good complexing properties compared to C-pivot lariat ethers compounds.[15]

On the other hand, pyrazolic derivatives have found several applications in pharmacology. These compounds can act as antitumoral,[16] antiviral,[17] and antimicrobial[18] agents. Nevertheless, and to the best of our knowledge, no study concerning the evaluation of the antibacterial activity of tetrapyrazolic macrocycles, has been reported in the literature.

In view of these observations and as continuation of our recent investigations of tetrapyrazolic macrocycles for the selective extraction of alkali cations,[6,19,20] we describe in the present work the synthesis of novel bifunctional tetrapyrazolic macrocycles. These have the same cavity size, but differ by the nature of the side arms. The effect on the percentage extraction of alkali metal cation was examined by the liquid-liquid extraction process and their antibacterial activity was screened by determining minimum inhibitory concentrations (MICs).

2. Results and discussion

2.1. Synthesis

The route used to prepare these macrocycles is shown in Scheme 1.

* Corresponding author.
E-mail addresses: f.malek@ump.ac.ma, fouad_malek@yahoo.fr (F. Malek).

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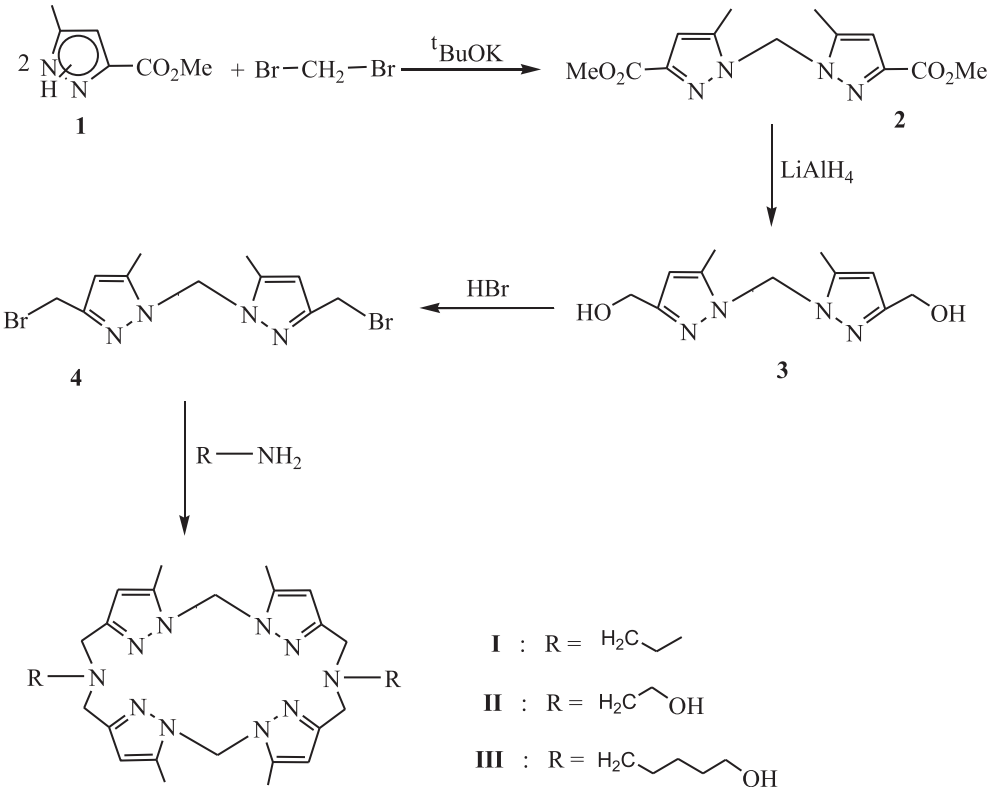
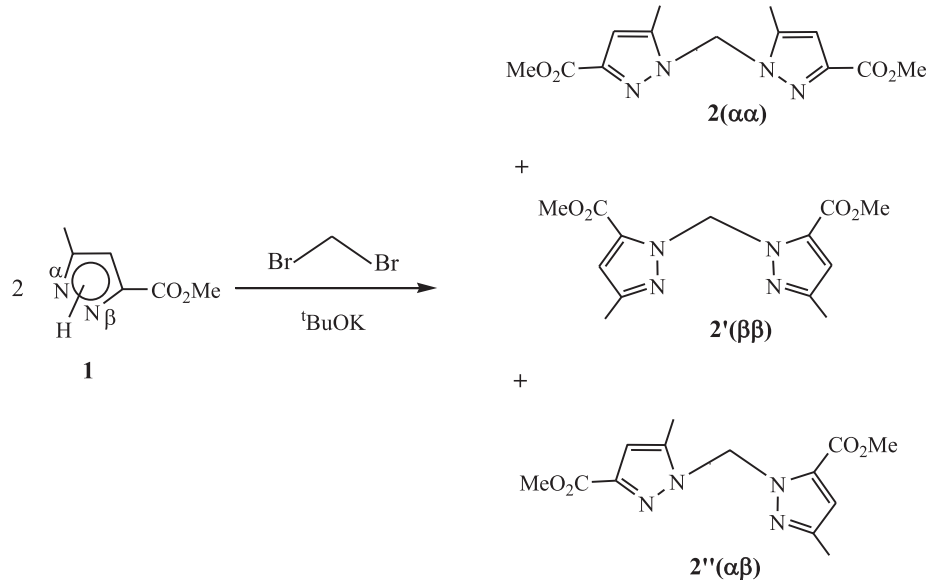


Scheme 1. Preparation steps of macrocycles.

The precursor **4** was firstly prepared in three steps. Its synthesis begins by condensation of two equivalents of the pyrazolic ester **1** with on equivalent of dibromomethane in the presence of ^{t}BuOK as base (Scheme 2). The obtained major product was the diester **2** due to αα attack according to the NMR ^{13}C[21], the coupling constants J (CH_3–H) and the solvent effect.[22] However, ββ and αβ attack can occur, and leads to the isomers **2′** and **2″** respectively (Scheme 2).

To verify the structure of the major product and ensure that it corresponds to the isomer **2**, X-ray crystallographic analysis was carried out on single crystals. Fig. 1 confirmed that the molecular structure of the major product was isomer **2**.

Compound **2** was then transformed to the hydroxy product **3** using lithium aluminium hydride ($LiAlH_4$). In contrast to our previous work,[6] this reaction was followed by the addition of hydrogen bromide solution (33 wt. % in acetic acid) to compound **3** to give our brominated synthon **4**, which is considered more reactive than the



Scheme 2. Structures of isomers.