

Proceeding Paper

Synthesis and Evaluation of Thiomethyl Substituted (4Z)-4-[(Pyrazol-4-yl)methylene]pyrazolone as an Optical Chemosensor [†]

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Abstract: Developing colorimetric devices for detecting chemical species is essential in many fields; nevertheless, developing effective chemosensors for many heavy and transition metal ions remains an important issue. As a result, in recent years, the use of colorimetric sensors for the selective and sensitive detection of metal ions has grown in popularity. Pyrazolones and its derivatives are heterocyclic compounds that have attracted interest due to their biological and pharmacological features. As a result, they have been used in various areas, including agriculture, medicine, organic synthesis, and analytical chemistry. However, the potential for chemosensing has yet to receive much attention. In this study, thiomethyl substituted (4Z)-4-[(pyrazol-4-yl)methylene]pyrazolone was synthesized, and its ability to act as an optical chemosensor for several metals was evaluated. According to preliminary results, this molecule could be an optical chemosensor to detect Fe³⁺, Sn²⁺, and Al³⁺.

Keywords: pyrazolones; optical chemosensors

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1. Introduction

Metal ions are essential for numerous biological processes, making them crucial for the maintenance of life [1]. Several heavy metal ions are commonly employed in industry or environmental applications [2–4] however, high concentration of these ions often have negative health or environment impacts. Aluminum, for example, is an important problem for agricultural plantations because it produces excessive acidity, which leads to reduced root and shoot growth, poorer biomass production, and disruption of physiological and metabolic processes, resulting in decreased crop yields [5,6]. Iron, on the other hand, is an essential element for plants and animals, playing an important part in biological processes; yet, the presence of ionic iron from industrial waste can cause poisoning and even the death of plants and animals [7]. Finally, while tin is useful in many sectors, excess amounts may be hazardous to health, causing respiratory, digestive, and neurological issues [8].

This highlights the importance of having strategies for detecting and measuring the concentration of these ions in various mediums. As a result, it is important to have novel compounds that work as more selective, sensitive, and quick response chemosensors for metal ions that may be detrimental to health or the environment.

Pyrazolones and their derivatives are heterocyclics that have attracted considerable attention because of their broad applications in areas such as coordination chemistry [9],

functional materials [10], and medicinal chemistry. Because of their broad spectrum of pharmacological properties, including antioxidant [11], anti-Alzheimer's [12], anticancer [13], and antibacterial activity [14], pyrazolones play an important part in drug development. These heterocycles have also been used to synthesize probes for the detection of various chemical compounds, biomolecules, and several metallic ions [15]. For example, several dipyrazolymethane derivatives were synthesized from 3-methyl-1-phenyl-2-pyrazolin-5-one and used as fluorescent probes for the detection of Cu^{2+} ions [16].

With these antecedents, we synthesized and studied several substituted (4Z)-4-[(pyrazol-4-yl)methylene]pyrazolones against different metal ions. In this work, we report the synthesis of thiomethyl substituted (4Z)-4-[(pyrazol-4-yl)methylene]pyrazolone and its evaluation as a chemosensor against different metals. According to preliminary results, this molecule could be an optical chemosensor to detect Fe^{3+} , Sn^{2+} , and Al^{3+} .

2. Materials and Methods

2.1. General

All solvents and reagents were from Sigma Aldrich and used without further purification. All melting points are uncorrected and were determined on a Büchi Melting Point M-560 apparatus. FTIR spectra were recorded by a Perkin Elmer FTIR Spectrum One by using ATR system ($4000\text{--}650\text{ cm}^{-1}$). The ^1H and ^{13}C NMR spectra were recorded at 298 K on a Bruker Advance 500 MHz spectrometer equipped with a z-gradient, triple-resonance (^1H , ^{13}C , ^{15}N) cryoprobe, using CDCl_3 as solvent. Chemical shifts are expressed in ppm with tetramethylsilane (TMS, $\delta = 0$ ppm) as an internal reference.

The 4,4'-(arylmethylene)bis(1H-pyrazol-5-ol) **1** and bis(spiropyrazolone)cyclopropane **2** precursors were prepared as previously reported [17, 18]. Reactions were monitored by TLC on silica gel using ethyl acetate/hexane mixtures as a solvent and compounds visualized by UV lamp. The reported yields are for the purified material and are not optimized.

2.2. Synthesis of (4Z)-4-[(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)(4-thiomethylphenyl)methylene]-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3)

The synthesis of the (4Z)-4-[(pyrazol-4-yl)methylene]pyrazolones **3** was adapted from a procedure reported by Dorofeeva and coworkers [19]. A suspension of 4 thiomethyl substituted bis(spiropyrazolone)cyclopropane **2** (1 mmol) in DMSO (0.5 mL) was rapidly heated to $100\text{ }^\circ\text{C}$ for 20 min and the progress of the reaction was followed by TLC in EtOAc/Hexane 1:2 until the reaction was complete. The reaction mixture was allowed to cool down to r.t. and the mixture was precipitated by slowly pouring the solution over an ice-water mixture. Finally, the mixture was allowed to stand at $4\text{ }^\circ\text{C}$ overnight. The orange precipitate formed was filtered, washed with cold water, and dried under vacuum. The pyrazolone **3** was obtained as an orange solid with a 96% yield. Mp $165\text{--}167\text{ }^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 1.53 (s, 6H, CH_3), 2.57 (s, 3H, SCH_3), 7.27 (d, $J = 8.4$ Hz, 2H, H3' and H5'), 7.30 (t, $J = 7.5$ Hz, 2H, H4), 7.36 (d, $J = 8.3$ Hz, 2H, H2' and H6'), 7.46 (t, $J = 8.0$ Hz, 4H, H3 and H5), 7.98 (dd, $J = 8.7, 1.0$ Hz, 4H, H2 and H6); ^{13}C NMR (126 MHz, CDCl_3) δ 15.2, 16.7, 113.2, 121.4, 125.5, 126.7, 129.0, 131.2, 136.2, 137.8, 143.4, 151.7, 157.9, 161.5; FTIR (cm^{-1}): 1591, 1483, 1374, 1311, 1012, 811, 751.

2.3. Preliminary Chemosensory Studies

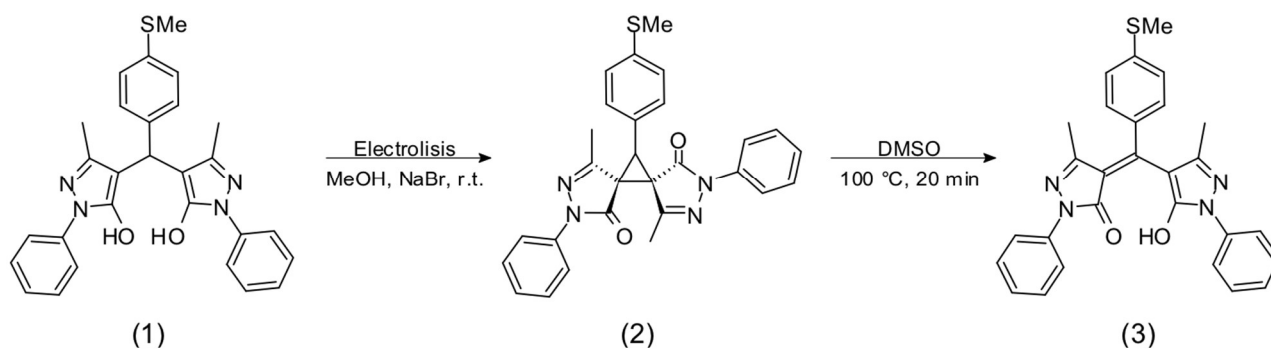
The pyrazolone **3** was dissolved into methanol to make a 2 mM stock solution. The stock solutions of the testing cation were prepared from CuCl_2 , $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, CaCl_2 , $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{Pb}(\text{NO}_3)_2$, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, HgCl_2 , ZnCl_2 and AlCl_3 dissolved in methanol (20 mM). All the solutions were stored at $-20\text{ }^\circ\text{C}$ and heated to room temperature before use. Previous to spectroscopic measurements, fresh solutions of the cations (1 mM) were prepared by diluting the stock solutions in methanol.

The UV-vis absorption spectra were determined in a 96-well plate, using a microplate reader Cytation 5 (BioTek) spectrophotometer. Absorption spectra of the pyrazolone **3** in the presence of various metal ions were measured in methanol solvent in the concentration of 100 μM and 25 μM , respectively.

3. Results and Discussion

3.1. Synthesis

The 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) **1** and bis(spiropyrazolone)cyclopropane **2** starting materials for the synthesis of **3** were obtained with a good yield using previously reported procedures. Bispyrazole **1** was synthesized after 15 minutes of reaction between 3-methyl-1-phenyl-2-pyrazolin-5-one and 4-(methylthio)benzaldehyde catalyzed by NaOAc [16]. Spirocyclopropane **2** was synthesized by electrolyzing a methanolic solution of **1** with NaBr for 5 hours at room temperature using an undivided cell (6 V, 800 mA D.C., graphite pencil lead as anode and iron wire as cathode) [17]. Finally, using the procedure reported by Dorofeeva et al. [18], pyrazolone **3** was synthesized in excellent yields by thermal isomerization of spirocyclopropane **2** in dimethyl sulfoxide (**Scheme 1**). The (4*Z*)-4-[(pyrazol-4-yl)methylene]pyrazolone **3** was characterized by using $^1\text{H-NMR}$ spectroscopy, and the spectroscopic data agrees with the expected structure.



Scheme 1. Synthesis of thiomethyl substituted (4*Z*)-4-[(pyrazol-4-yl)methylene]pyrazolone **3**.

3.2. Chemosensory Studies

The UV-vis absorption spectrum of a methanolic solution 100 μM of pyrazolone **3** with and without the presence of various metal cations, such as Cu^{2+} , Co^{2+} , Mn^{2+} , Fe^{3+} , Ni^{2+} , Ca^{2+} , Sn^{2+} , Pb^{2+} , Fe^{2+} , Hg^{2+} , Zn^{2+} , and Al^{3+} (25 μM in methanol), was measured using a Cytation 5 (BioTek) spectrophotometer. The spectra of free ligand **3** show two strong absorption bands at 360 nm and 480 nm (Figure 1). The same bands are present after the metal ions are added, except for Fe^{3+} , Sn^{2+} , and Al^{3+} , which show a bathochromic shift of the peak from 360 nm to 390 nm and a reduction in the absorbance of the peak at 480 nm.

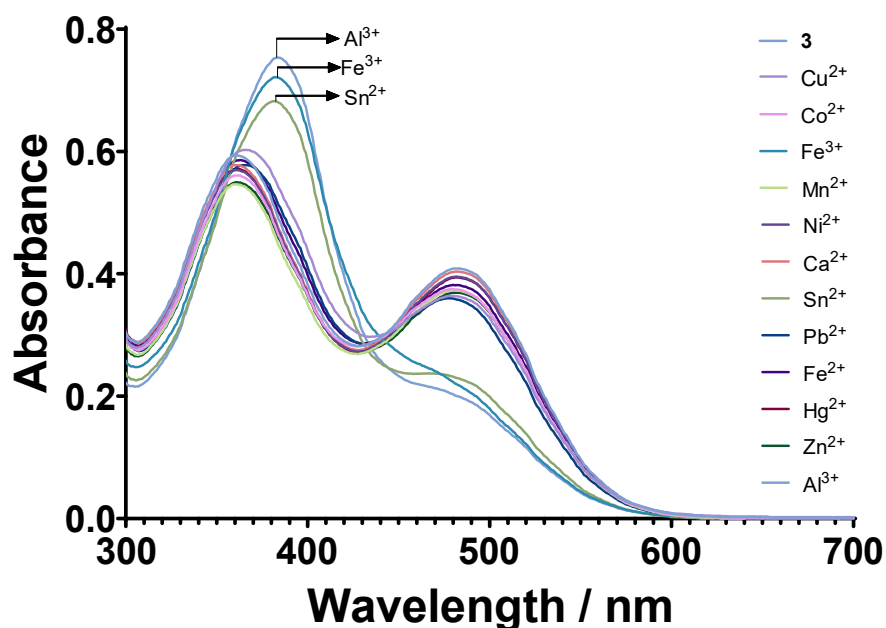


Figure 1. UV–vis absorbance spectra of **3** (100 μM). Free ligand and ligand in presence of different metal ions (Cu^{2+} , Co^{2+} , Mn^{2+} , Fe^{3+} , Ni^{2+} , Ca^{2+} , Sn^{2+} , Pb^{2+} , Fe^{2+} , Hg^{2+} , Zn^{2+} , and Al^{3+}) (25 μM) in methanol solvent.

The absorbance response of **3** to various concentrations of Fe^{3+} , Sn^{2+} , and Al^{3+} was investigated. With increasing concentration of these ions, all solutions' absorbance intensity at 480 nm gradually decreases (Figure 2).

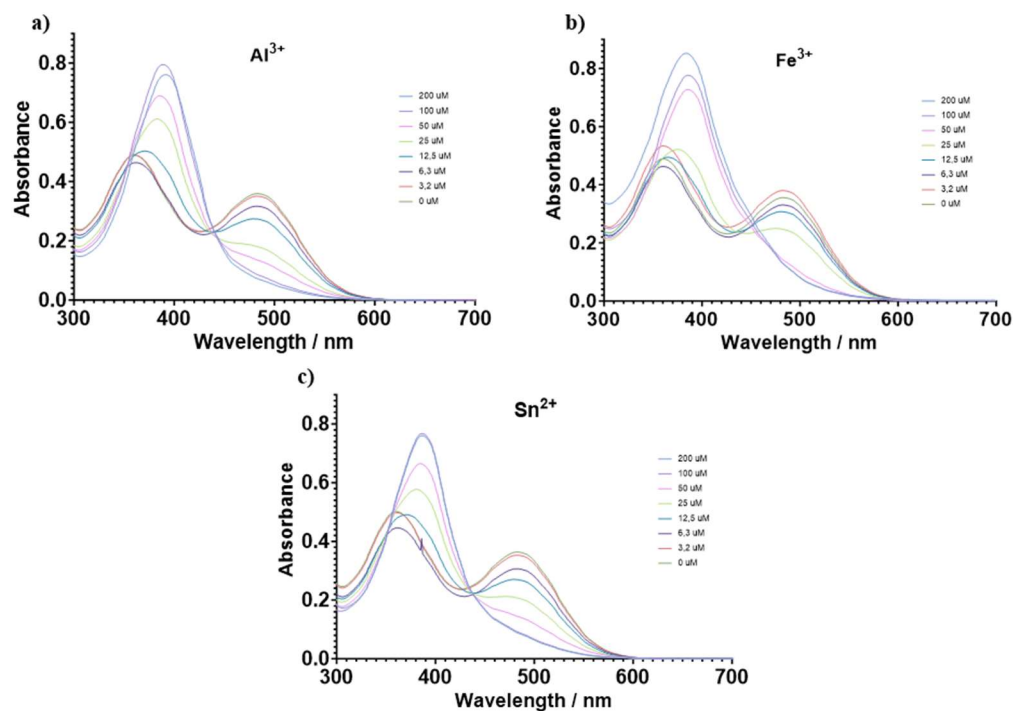


Figure 2. Spectrophotometric titration of pyrazolone **3** with addition of increasing amount of metallic ions (0–200 μM) in MeOH. (a) Al^{3+} , (b) Fe^{3+} , and (c) Sn^{2+} .

4. Conclusions

The synthesis and evaluation of thiomethyl substituted (4Z)-4-[(pyrazol-4-yl)methylene]pyrazolone **3** as a colorimetric sensor for different metallic cations is presented in this research. In the presence of Fe³⁺, Sn²⁺, or Al³⁺, the absorbance spectra of **3** show a bathochromic shift of the principal peak from 360 nm to 390 nm and a reduction of the peak at 480 nm. Both effects depend on ion concentration, suggesting that this molecule could be used as an optical chemosensor to detect these cations.

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