Polyhedron 99 (2015) 59–70

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Molecular design and the optimum synthetic route of the compounds with multi-pyrazole and its derivatives and the potential application in antibacterial agents

Ji-Xiao Wang [a], Zi-Ran Zhu [b], Feng-Ying Bai [c,*], Xin-Yu Wang [a], Xiao-Xi Zhang [a], Yong-Heng Xing [a,*]

[a] College of Chemistry and Chemical Engineering, Liaoning Normal University, Huanghe Road 850#, Dalian City 116029, PR China
[b] Department of Biochemistry, Dalian Medical University, Dalian 116044, PR China
[c] College of Life Science, Liaoning Normal University, Dalian 116029, PR China

ARTICLE INFO

Article history:
Received 22 April 2015
Accepted 12 June 2015
Available online 25 June 2015

Keywords:
Pyrazole and its derivatives
N-heterocyclic ligands
Antibacterial activity
Crystal structure
Spectra properties

ABSTRACT

Molecular design and efficient synthetic procedures have been developed for pyrazole and its derivatives with different linkers. In particular, twelve compounds with –I or $–NO_2$ substituted groups on the pyrazole ring were synthesized for the first time. These compounds are characterized by element analysis, IR, HNMR, M.P. and X-ray diffraction. In addition, some compounds and corresponding complexes were also assayed in vitro for their ability to inhibit the growth of representative Gram-positive bacteria, Gram-negative bacteria and the fungus. It was worthwhile to note that some compounds could be used as potential antibacterial agents.

1. Introduction

Pyrazole and its derivatives as a crucial family member of N-heterocyclic ligands are used as pesticides and medicinal preparations because of their high biological activities [1–4]. In the mean time, it is also found widespread applications in the fields of supramolecular chemistry, crystal engineering, materials sciences, sensors, biochemistry, catalysis etc. [5–12]. In the recent years, with the further study of multidentate ligands, there is a growing interest in molecular design of multi-pyrazole compounds and its derivatives due to larger π-conjugated system, good planarity and stable structure [13–17]. During the past two decades, some complexes with multi-pyrazolyl compound as ligands have been reported, for instance, $[Zn(L_2)(SCN)_2]$ (L_2 = 1,4-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzene), Co(bpz*eaT)$(SCN)_2$ (bpz*eaT: 2,4-dimethyl-1H-pyrazol-1-yl)-6-diethylamino-1,3,5-triazine), $[Ag_2(Lp)_{1.5}(NO_3)](NO_3)$ $[Cu_2(\mu\text{-}Lp)(H_2O)_6](SiF_6)_2{\cdot}(H_2O)_4$ Ag(μ-Lp)NO_3 (Lp = p-$[CH(pz)_2]_2C_6H_4$), Hg(TpzT)$(SCN)_2{\cdot}H_2O$ (TPzT: 2,4,6-tri(pyrazole-1-yl)-1,3,5-triazine), etc. [18–22]. Most of the complexes were reported about their characteristics, including spectrum, structures, thermal properties, luminescent properties and synthesis. However, there are few investigations about biological activity for the complexes with multi-pyrazole and its derivatives as ligands. Obviously, it became a hot issue that efficiently synthesizing of multi-pyrazole and its derivatives compounds for exploring the application of the complexes in the field of biochemistry.

Here, we have synthesized firstly twelve multi-pyrazolyl compounds with –I or $–NO_2$ substituted groups and explored a series of optimization synthetic procedures for preparing multi-pyrazolyl compounds by the reaction of pyrazole and its derivatives with different linkers in two kinds of solvents: dimethylsulfoxide (DMSO)-potassium hydroxide (KOH) and tetrahydrofuran (THF). Compared with traditional procedures [23–30], we have achieved the goals of maximizing reaction efficiency and minimizing chemical wastes. We have developed four types synthetic system, including multi-pyrazolyl compounds (scheme 1): alkane–pyrazole derivatives, benzene–dipyrazole derivatives and benzene–tetrapyrazole derivatives in the superbasic DMSO-KOH medium; triazine–pyrazole derivatives in the THF. In addition, in long time for exploring synthetic procedures, we found that steric hindrance, substituted groups and the condition of the reaction play a vital role in the targets of separating high yield and purity compounds. At the same time, some new compounds and the complexes reported by our group are assayed in vitro for their biological activity and some of them exhibit excellent ability of antibacterial activity.

* Corresponding authors.
E-mail addresses: baifengying2003@163.com (F.-Y. Bai), xingyongheng2000@163.com (Y.-H. Xing).

http://dx.doi.org/10.1016/j.poly.2015.06.020
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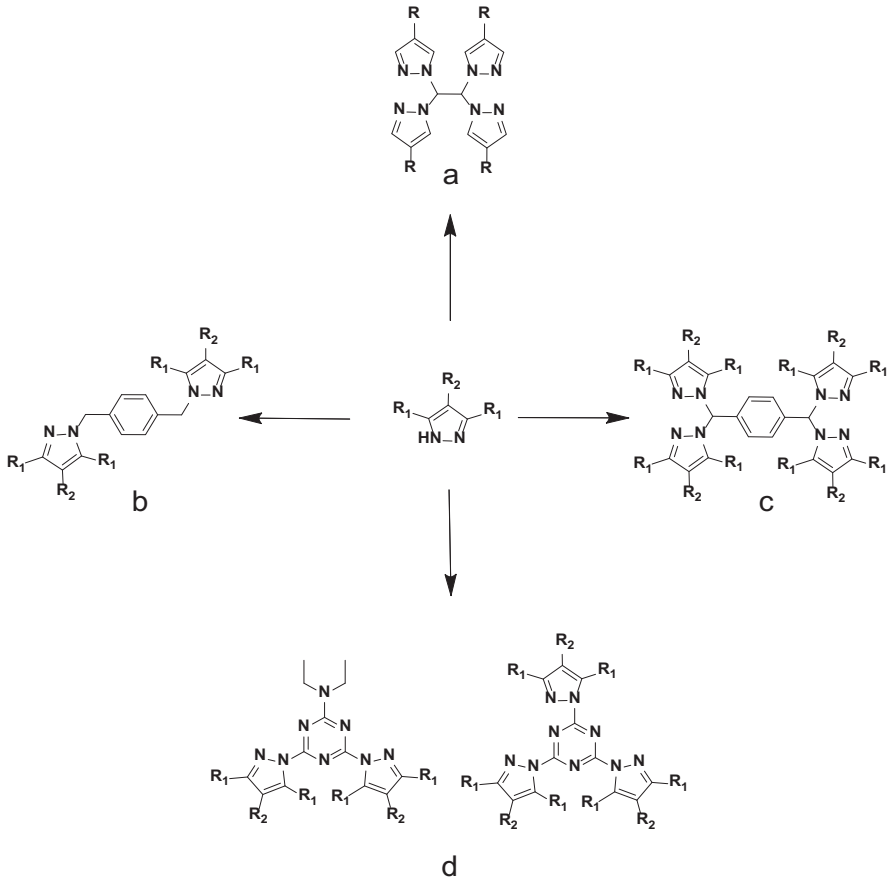

Scheme 1. Four kinds of pyrazole and its derivatives: (a) alkane–pyrazole derivatives; (b) benzene–dipyrazole derivatives; (c) benzene–tetrapyrazole derivatives; (d) triazine–pyrazole derivatives.

2. Results and discussion

2.1. Synthesis

We began to explore the optimum synthetic route of alkane–pyrazole derivatives by controlling the reaction of pyrazole (Scheme 2), 1,1,2,2-tetrabromoethane (TBE) and potassium hydroxide (KOH) in 4:1:4 molar ratios and prolonging deprotonation reaction time in the mixed system of pyrazole and KOH in dimethylsulfoxide (DMSO) at 80 °C. That is the solution of TBE in DMSO was added dropwise into mixed solution and stirred continuously for 5 h. Through a series of follow-up treatments, the target product **1a** was obtained in 71.4%, which was much higher yield and low side reactions with TBE than that reported in literature [24]. To obtain high yield and reduce reaction time of compound **1c**, we attempted to choose 4-iodo-*1H*-pyrazole as nucleophile to replace starting material "**1a**" in the literature [23] to synthesize "**1c**", and the synthetic condition was similar to that of compound **1a**, the result found that we have obtained successfully target product **1c** and achieved expected yield.

In addition, we have also studied the optimum synthetic method of benzene–dipyrazole derivatives and corresponding complexes [31] (Scheme 3). That is the mixture of pyrazole (or its derivatives) and KOH in DMSO was vigorous stirred for making pyrazole complete deprotonation and then reacted with the solution of 1,4-bis(bromomethyl)benzene in DMSO. After a series of following steps, we obtained compounds **2a** and **2b**. It was considered that 1H-pyrazole occurs readily iodination (nitration) substituted reaction on the C4 atom and coordination modes of the compounds would be varied via introduction of different substituents onto the pyrazole rings, we choose pyrazole derivatives with iodination or nitration group as nucleophile and synthesized successfully four new compounds **2c**-**2f** with –I and NO_2 groups by the similar synthetic method of the compounds **2a**-**2b**.

The facile methods of synthesizing benzene–tetrapyrazole derivatives were shown in Scheme 4. The optimization route ideology was similar to that of alkane–pyrazole derivatives: that is controlling primary materials molar ratio and prolonging completely deprotonation reaction time. We obtained higher yields and the products, which were readily isolated by dilution with water and filtration. The additional advantages was avoiding the use of toxic phosgene in the traditional route, shortening the reaction time of pyrazole with 1,4-bis(dibromomethyl)benzene and the procedure was more benign from the ecological viewpoint. In addition, we also chosen pyrazole derivatives with –I and NO_2 groups as nucleophile to synthesize successfully a series of new compounds **3c**–**3f**. Through a lot of experimental results, we found that substituted groups and steric hindrance from different substituted groups on the pyrazole ring play a vital role in synthesizing benzene–dipyrazole/tetrapyrazole derivatives. So, synthesizing of the corresponding compounds with CH_3 group on the pyrazole ring would be more difficult than the other compounds and need more time. In addition, it needed more time to synthesize benzene–tetrapyrazole derivatives compounds due to the increasing number of pyrazole and its derivatives.

In order to further investigate synthetic method and explore new compounds, we have also studied the synthetic procedures of 1,3,5-triazine–pyrazole derivatives. The triazine–pyrazole