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Facile Synthesis of 1,6-Bis(2-furyl)-2,5-bis(2-hydroxy-3-formyl-5methylbenzyl)-2,5-diazahexane: a New Dinucleating Ligand

Gang-Chun Sun¹, Zhan-Hang He², Zhong-Jun Li², Xiao-Dong Yuan³, Zhi-Juan Yang², Guo-Xi Wang⁴, Liu-Fang Wang^{1*} and Chang-Rang Liu^{2,*}

¹ National Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, China; E-mail:sungangchun@371.net.

² Department of Chemistry, Zhengzhou University, ZhengZhou 450052, China.

³ Department of Applied Oil Engineering, Logistical Engineering University, Chongqing 400042, China.

⁴ Department of Chemical Engineering, Anyang University, Anyang 455000, China.

*Author to whom correspondence should be addressed; E-mail: llyyjz@public.lz.gs.cn

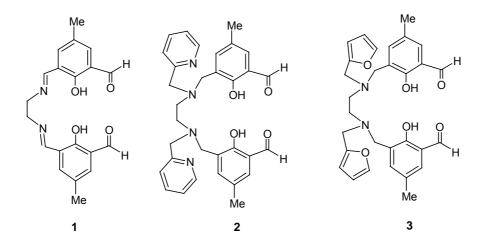
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Abstract: A convenient three-step preparation of the dinucleating ligand, 1,6-bis(2-furyl)-2,5-bis(2-hydroxy-3-formyl-5-methylbenzyl)-2,5-diazahexane (**3**) starting from 2,6-bis(hydroxymethyl)-4-methylphenol (**4**) is reported. Compound **4** was partially oxidized with preactivated manganese dioxide to form compound **5**, which was converted to 2-hydroxy-3-chloromethyl-5-ethylbenzaldehyde (**6**) with conc.HCl/EtOH. Compound **6** in turn reacted with N,N'-bis (2-furyl)-1,2-diaminoethane (**7**) in the presence of K₂CO₃ in ethanol to give the title compound **3**. No protecting groups were required in the whole process and the conditions were mild.

Keywords: Synthesis, Dinucleating ligand, 2,5-Diazahexane derivative, Partial oxididation, Manganese dioxide.

Introduction

The design and synthesis of dinucleating ligands that incorporate similar or dissimilar metal ions to form dinuclear complexes is of importance in attempts to mimic the active sites of metalloenzymes, to search for appropriate systems for binding and activating small molecules and for investigating the mutual influences of two metal centers on the electronic, magnetic and the electronical properties of such dinuclear systems [1-3]. Compound 1 [4] is a well known dinucleating ligand which can act as a precursor of many macrocyclic di- or multinucleating ligands since it can easily react with diamines, and much effort has gone into synthesizing its derivatives such as compounds 2 and 3, both of which can been viewed as the ligands of the same type. It was also reported that when saturation of the azomethine linkage and/or the introduction of some groups to the lateral chains of these acyclic or macrocyclic ligands were carried out in the hope of obtaining di- or multinucleating complexes of particular desired structures, the changes had significant effects upon the stereochemistry and redox as well as other properties [5] of the metal ions of the complexes. When we first set out to obtain analogues of ligand 2 we examined the published method, which involved a lengthy route [6]. Consequently we sought to both shorten the synthetic sequence and at the same time simplify the manipulations required. We now report the successful synthesis of a new ligand 3, similar in structure to compound 2, but obtained by a novel method This new route has the potential of facilitating the synthesis of other analogues of compounds 2 and 3 with similar structural features.



Results and Discussion

The new three-step synthetic procedure followed is shown in Scheme 1. Using preactivated manganese dioxide as a selective partial oxidation agent [7], which can oxidize only one hydroxymethyl group to a formyl group, 2,6-bis(hydroxymethyl)-4-methylphenol (4) [8] was converted to 5 in chloroform at room temperature in 38% yield (lit. [7] yield 40%). This step took place under mild conditions and was easy to work up. Compound 5 was efficiently chlorinated to 6 in the presence of concentrated hydrochloric acid while the formyl and the phenolic hydroxy groups remained untouched. Coupling of benzyl chloride 6 with diamine 7 [9] under mild conditions gave the

title compound 3 with a yield of 42%. Although the yields of the first and third steps are not as high as those previously reported, mainly because of the reactivity of the phenol derivatives 4 and 6, the fact that no protecting groups were required makes this method quite attractive in view of the significant simplification of the overall sequence that it represents.

As noted, the previously reported preparation of compound 2, similar in structure to 3, involves nine steps [6]. Although the yields of each step in the earlier synthesis were relatively high (ranging from 60% to nearly 100%), thus highlighting both the effectiveness of the use of protecting groups and the elegance of the overall synthetic scheme, the final yield was not as high (about 22%) because of the large number of steps involved. Furthermore, the procedure was cumbersome, requiring some reagents which may be hard to obtain and expensive and some severe reaction conditions. The sequence now presented gave compound 3 in higher yield by a shorter route starting from a common starting material 4, mainly due to the fact that protecting groups were not used (and consequently did not have to be removed). The reaction conditions were mild too.

In the ¹H-NMR spectrum of compound **3** the signals belonging to the protons of the phenolic hydroxy groups were broad which showed that the protons were acidic, and suggesting formation of some O-H---N hydrogen bonds. This phenomenon has been observed in some similar systems [10,11] and will be further confirmed by single crystal X-ray diffraction which will be reported elsewhere.

ŌН OH OH OH OH CI OH Ή а b 38% 95% Me Me Me 4 5 6 С 2 3 42% Me 7 6

a). MnO₂/CHCl₃; b). conc.HCl/EtOH; c). K₂CO₃/EtOH

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Scheme I

Experimental

General

Melting points were determined using a WC-1 melting point apparatus. ¹H-NMR spectra were recorded on Bruker DPX400 spectrometer using TMS as internal reference (chemical shifts reported in δ ppm) and IR spectra on a Shimadzu IR435 infrared spectrometer (v_{max} in cm⁻¹). Elemental analyses were performed on a Carlo-Erba 1106 C, H and N analyzer. 2,6-Bis(hydroxymethyl)-4-methylphenol (4) [8] and N,N'-bis(2-furyl)-1,2-diaminoethane (7) [9] were prepared according to the reported methods. Other reagents were all obtained commercially. MnO₂ was kept in a muffle oven at a temperature of 300 to 320°C for 12 h until just prior to use.

2-Hydroxy-3-hydroxymethyl-5-methylbenzaldehyde (5).

This compound was synthesized by a modification of the previously reported method [7]. 2,6-Bis(hydroxymethyl)-4-methylphenol (4) (20g, 0.12mol) was placed in a 500 mL flask and stirred with a suspension of MnO₂ (100g, 1.14mol) in CHCl₃ (300mL) for 16 h at room temperature. The mixture was filtered and washed with CHCl₃ for several times until the filtrate became colourless. The solvent was removed and the residue was recrystallized from EtOH/H₂O (1:3, v:v) to give yellowish needles (yield: 7.6g, 38%). M.p. 72-73° (lit. [7] 75-76°C). Anal. Calc for C₉H₁₀O₃: C: 65.05%, H: 6.07%; Found: C: 64.66%, H: 5.92%.

2-Hydroxy-3-chloromethyl-5-methylbenzaldehyde (6).

A solution of compound **5** (5 g, 0.03mol) in alcohol (25 mL) was added dropwise with stirring into a 250 mL flask containing conc. HCl (75 mL) placed in a 40°C water bath. The mixture was stirred for about 2 h, then filtered and washed with water until the pH was ~7 to give 4.8g (95%) of white needles (m.p. 92-93°C). Anal. Calc. for C₉H₉O₂Cl: C: 58.55%, H: 4.91%; Found: C: 58.84%, H: 4.96%; ¹H-NMR (CDCl₃/400MHz) \overline{o} : 2.35 (s, 3H), 4.67 (s, 2H), 7.31 (d, 1H), 7.46 (d, 1H), 9.87 (s, 1H), 11.26 (s, 1H). IR (KBr): 1661, 1599, 1469, 875 cm⁻¹.

1,6-Bis(2-furyl)-2,5-bis(2-hydroxy-3-formyl-5-methylbenzyl)-2,5-diazahexane (3).

Compound **6** (4.1 g, 0.022mol) in ethanol (80mL) and anhydrous K_2CO_3 (5.5 g, 0.04mol) were placed in a 250mL flask, then compound **7** (2.2 g, 0.01mol) in ethanol (20mL) was added dropwise at room temperature. The mixture was stirred for 6 h at 40°C, then quenched and acdified to pH~2 with 5% aqueous HCl. Most of the solvent was removed by concentration *in vacuo* and the residue was taken up in water (50mL). After filtration the filtrate was taken to pH~9 with 1:1 ammonia/water thus forming a yellowish colloidal precipitate. After leaving the mixture standing overnight, the crude product was filtered and washed with water to pH~7. Recrystallization from 95% ethanol gave

compound **3** (2.17 g, 42%) as off-white needles (m.p. 109-110°C). Anal. Calc. for $C_{30}H_{32}N_2O_6$: C: 69.78%; H: 6.20%; N: 5.43%). Found: C: 69.59%; H: 6.45%; N: 5.44%. ¹H-NMR (CDCl₃/400MHz) δ : 2.26 (s, 6H), 2.71 (s, 4H), 3.66 (s, 4H), 3.69 (s, 4H), 6.17 (d, 2H), 6.31 (s, 2H), 7.27 (d, 2H), 7.37 (s, 4H), 10.17 (s, 2H), 11.25 (br, 2H). IR (KBr): 2859, 1676, 1605, 1500, 1454, 874 cm⁻¹.

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Sample Availability: Compounds 3, 5, 6, 7 are available from MDPI and the authors

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