

The Preparation of Dicompartmental Multifunctional Group Ligands

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A convenient method for the preparation of the phenol-based ligands 1,6-bis(2-thiophenyl)-2, 5-bis(2-hydroxy-3-hydroxymethyl-5-methylbenzyl)-2, 5-diazahexane and 1,6-bis(5-methyl-2-thiophenyl)-2,5-bis(2-hydroxy-3-hydroxymethyl-5-methylbenzyl)-2,5-diazahexane possessing two dissimilar compartments having multifunctional groups is reported. To synthesize these ligands, an equivalent of 1,6-bis(2-thiophene)-2,5-diazahexane or 1,6-bis(5-methyl-2-thiophene)-2,5-diazahexane and two equivalents of 2,2-dimethyl-6-methyl-8-(chloromethyl)benzo-1,3-dioxin were reacted in the presence of Na₂CO₃ in 1,4-dioxane, followed by acid hydrolysis of an acetonide-protecting group. Characterization data for the new compounds is reported.

Keywords Acyclic ligand; compartmental ligand; multifunctional ligand; phenol-based ligand; synthesis

INTRODUCTION

Phenol-based binucleating ligands containing two different compartments have received attention because of their capability to bind two different metal centers in close proximity.^{1–8} Since unsymmetrical dicompartmental ligands are of importance for providing discrete heterodinuclear core complexes, various types of compartmental ligands including the end-off, side-off, and their macrocyclic type have been developed.^{9–11} They have a basic structure of type **1** (Figure 1) where "B" is an electron-pair donating atom. The introduction of donor auxiliary "A" residues to the two amino nitrogen atoms in **1** provides new unsymmetrical compartmental ligands of type **2**. A synthetic method

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FIGURE 1 (I) and (II) examples of dicompartmental ligands reported in the literature. (III) the dicompartmental ligands reported in this paper.

for the preparation of compounds **2** with pyridyl groups "A" and two dialdehyde groups "B" was reported by Fraser et al.⁶ and is based upon nine consecutive steps. In this report we describe a successful four-step reaction leading to the new ligands **3a** and **3b**. This route has the potential of facilitating the synthesis of other analogues of compound **3**.

RESULTS AND DISCUSSION

The acyclic dialcohols **3a** and **3b** were prepared by the sequence steps outlined in Scheme 1. First, the diamine moiety of the desired compound was prepared by the condensation of ethylenediamine with two equivalents of 2-thiophenealdehyde or 5-methyl 2-thiophenealdehyde at r.t. under aerated conditions, which resulted in the formation of the crystalline diimine compounds 4a and 4b in a 92-96% yield. These compounds are sufficiently pure (95% based on ¹H NMR) for further treatment. Subsequently, these diimine compounds were converted to their diamine counterparts **5a** and **5b** quantitatively by NaBH₄ as a reducing agent. The infrared spectra of the imine and amine compounds are generally similar. The main spectral differences between the imines and amines are the emergence of a sharp but weak band at 3268 cm^{-1} . which is attributed to the N-H stretch of the quaternized amine and the disappearance of the strong band at 1643 cm^{-1} , which corresponds to the C=N stretch of the imine groups.¹² A band near 1550 cm⁻¹ for compounds **4a** and **5a** is assigned to the skeletal vibration of the aromatic



a, HCHO, aq NaOH; b, CH₃C(OCH₃)=CH₂, cat. CH₃SO₃H, THF; c, *N*-chlorosuccinimide,

Me₂S, CH₂Cl₂; d, EtOH; e, NaBH₄, EtOH; f,(i) Na₂CO₃, 1,4-dioxane, (ii) aq. HCl, CH₂Cl₂.

SCHEME 1

rings.¹³ Also, the ¹H NMR spectrum of diimines **4** shows a singlet at 8.21 ppm corresponding to the proton attached to the imine moiety. However, the amine shows a singlet for the CH_2 moiety attached to the nitrogen in the ¹H NMR spectrum at 2.36 ppm. On the other hand, the triol **7** and its protected derivative **8** were made by a method described by Fraser et al.¹⁴ In the next step, **8** was chlorinated efficiently by the Corey procedure.¹⁵ Finally, the coupling of benzyl chloride **9** with diamine **5** under mild conditions followed by acid hydrolysis of the acetonide protecting group afforded dialcohol ligands **3a** or **3b** in yields of 54–94%.

The IR spectra of both **3a** and **3b** were similar and showed a weak band at around 3300 cm⁻¹, which is probably attributed to the OH stretch of the alcoholic groups. The total yields of the final products **3a** and **3b** are typically lower than 20% and 35%, respectively. These yields are limited mainly by the preparation of triol **7** (yield 51%) and by the condensation reaction of **5a** with **9** (yield 54%). The major reason for the low yield in the formation of **3a** is the polymerization of compound **5b** under the applied reaction condition. It has been proven that the unsubstituted α -position in thiophene is susceptible for polymerization.¹⁶ In fact, using compound **5b**, in which the α -position is substituted by a methyl group, resulted in a significant increase in the yield of the condensation reaction (95%). In the ¹H NMR spectra of compounds **3a** and **3b**, the signals belonging to the protons of the phenolic hydroxy groups were broad. This indicates that the protons are acidic and suggests the formation of O-H–N hydrogen bonds. This phenomenon has been observed in similar systems¹⁷ and was also confirmed by single crystal X-ray diffraction.¹⁸

It can be concluded that the dissimilar two compartmental ligands **3** were prepared in satisfactory yields by a simple and convenient multistep method.

EXPERIMENTAL

All elemental analyses were performed on a LECO CHN-600 elemental analyzer. ¹H NMR spectra were recorded on a Bruker 300 fourier transform spectrometer. Infrared spectra were recorded in KBr pellets with a single beam Bruker VECTOR22 FTIR instrument. Mass spectra were obtained on a VG 70E double-focusing high-resolution spectrometer. All samples were dried to constant weight under high vacuum prior to analysis. Compounds 2,6-bis(hydroxymethyl)-4-methylphenol,¹⁴ 2,2-dimethyl-6-methyl-8-(hydroxymethyl)benzo-1,3-dioxin,¹⁴ and 1,6-bis(2-thiophene)-2,5-diazahexane¹⁹ were prepared by standard methods. All reagents were commercial materials. Solvents used were dried over CaH₂ (CH₂Cl₂), LiAlH₄ (ether and dioxane), and K (THF).

N,*N*'-Bis(5-methyl-2-thiophenemethyl)-1,2-ethanediamine (4b) and 1,6-Bis(5-methyl-2-thiophenyl)-2,5-diazahexane (5b)

The diimine compound **4b** and its diamine counterpart **5b** were prepared by procedures similar to those described by Patra and Goldberg¹⁹ using 5-methyl-2-thiophenealdehyde instead of 2-thiophenealdehyde as a starting material. The desired diimine was obtained as a brown solid (96%), and the diamine was obtained as a light-brown liquid with a quantitative yield. **4b**: m.p.: 44–45°C. IR: strong band at 1643 cm⁻¹. ¹H NMR (300.13 MHz, CDCl₃) δ : 2.54 (s, 6H, Thiophene-CH₃), 3.83 (s, 4H, N–CH₂), 6.67 (d, J = 4.6 Hz, 2H, thiophene-H), 7.03 (d, J = 4.6 Hz, 2H, thiophene-H), 8.21 (s, 2H, N=CH). Anal. calcd. for C₁₄H₁₆N₂S₂: C, 60.83; H, 5.83; N, 10.13%. Found: C, 60.54; H, 5.50; N 10.33%. **5b**: IR: medium band at 3268 cm⁻¹. ¹H NMR (300.13 MHz, CDCl₃) δ :1.56 (br. s, 2H, N-H), 2.36 (s, 4H, -CH₂-thiophene), 2.69 (s, 6H, thiophene-CH₃), 3.81 (s, 4H, -CH₂-CH₂-), 6.49 (d, J=3.8 Hz, 2H, thiophene-H), 6.60

(d, J = 3.8 Hz, 2H, thiophene-**H**). Anal. calcd. for $C_{14}H_{20} N_2S_2$: C, 59.96; H, 7.19; N, 9.99%. Found: C, 60.21; H, 7.50; N, 9.77%.

2,2-Dimethyl-6-methyl-8-(chloromethyl)benzo-1,3-dioxine (9)

A stirred solution of N-chlorosuccinimide (7.61 g, 57.0 mmol) in dry distilled CH₂Cl₂ (200 mL) in a fume hood was cooled to 0°C, and dimethylsulfide (37.0 g, 600 mmol) was added dropwise. The resulting colorless reaction mixture was further cooled to -25° C, and 2,2-dimethyl-6methyl-8-(hydroxymethyl)benzo-1,3-dioxine 8 (11.30 g, 50.0 mmol) in dry distilled CH₂Cl₂ (10 mL) was added slowly dropwise. After stirring at 0° C for 2 h, the resulting reaction mixture was poured into cold brine $(\sim 200 \text{ mL})$, the aqueous layer was extracted with Et₂O (2 × 50 mL), and the combined organic layers were dried over anhydrous Na₂SO₄. The filtration and concentration under reduced pressure gave a crude product as yellow oil. The crude compound was dissolved in a minimal amount of Et_2O : *n*-hexane (1:1) mixture, loaded onto a short column (1 inch diameter) containing silicagel (20 g), and eluted with Et₂O: *n*-hexane (1:1). The desired compound came out with the first fraction. The concentration of the eluent under reduced pressure gave pure compound 9 as yellow oil, 10.3 g (85%). ¹H NMR (300.13 MHz, CDCl₃) δ: 1.54 (s, 6H, C-CH₃), 2.26 (s, 3H, Ar-CH₃), 4.57 (s, 2H, ArCH₂-Cl), 4.80 (s, 2H, ArCH₂-O), 6.76 (s, 1H, Ar-H), 7.04 (s, 1H, Ar-H). The high-resolution mass spectrum showed the main peak at m/z 226.0756 corresponding to the molecular formula of C₁₂H₁₅O₂Cl. FT-IR (KBr): 1445 cm⁻¹ (aromatic skeleton).

1,6-Bis(2-thiophenyl)-2,5-bis(2-hydroxy-3-hydroxymethyl-5methylbenzyl)-2,5-diazahexane(3a)

1,6-bis(2-thiophenyl)-2,5-diazahexane **5a** (0.512 g, 2.0 mmol) and 2,2-dimethyl-6-methyl-8-(chloromethyl)benzo-1,3-dioxine **9** (1.00 g, 4.1 mmol) were dissolved under argon in dry distilled 1,4-dioxane (30 mL), and anhydrous Na₂CO₃ (1.900 g, 17.9 mmol) was added. The reaction mixture was stirred at 100°C for 2 days, allowed to cool to r.t., and then filtered through Celite. Dioxane was removed in vacuo to give a viscous orange-brown oil, which was treated with aqueous HCl (1.16 M, 50 mL) and heated on a steam bath for 10 min. After cooling, the yellow suspension was extracted with Et₂O (4 × 20 mL). The aqueous layer was adjusted to pH \approx 7.0 with aqueous NaOH (1 M) and then to pH \approx 8.4 by an addition of saturated aqueous NaHCO₃. The oily mixture was extracted with CH₂Cl₂(8 × 10 mL), and the combined organic extracts were dried over Na₂SO₄. The filtration and concentration under

reduced pressure gave **3a** as pale-brown oil (ca. 85% by ¹H NMR) that slowly solidified, 0.64 g, (54%). ¹H NMR (300.13 MHz, CDCl₃) δ :1.73 (t, J = 5.7 Hz, 2H, Ar-CH₂-OH), 2.60 (s, 6H, Ar-CH₃), 2.79 (s, 4H, N-CH₂-thiophene), 3.75 (s, 4H, N-CH₂-Ph), 3.88 (s, 4H, N-CH₂-CH₂-N), 4.54 (d, J = 5.7 Hz, 4H, Ar-CH₂-OH), 6.97 (s, 2H, Ar-H), 6.98 (s, 2H, Ar-H), 6.97–7.46 (m, 6H, thiophene-H), 11.00 (br. s, 2H, Ar-OH). When one drop of D₂O was added to the ¹H NMR sample, the signals at 11.00 and 1.73 ppm disappeared, and the doublet at 4.54 ppm sharpened into a singlet at 4.53 ppm. The high-resolution mass spectrum showed the main peak at m/z = 552.2132 corresponding to a monopositively charged compound. Anal. calcd. for C₃₀H₃₆N₂O₄S₂: C, 65.19; H, 6.56; N, 5.07. Found: C, 65.01; H, 6.78; N, 5.21.

1,6-Bis(5-methyl-2-thiophenyl)-2,5-bis(2-hydroxy-3hydroxymethyl-5-methylbenzyl)-2,5-diazahexane (3b)

Compound **3b** was prepared in the manner as previously described for the preparation of **3a** using 1,6-bis(5-methyl-2-thiophene)-2,5diazahexane instead of 1,6-bis(2-thiophenyl)-2,6-diazahexane. Compound **3b** was obtained as a pale-brown solid (94%). ¹H NMR (300.13 MHz, CDCl₃) δ : 1.70 (t, J = 5.5 Hz, 2H, Ar-CH₂-OH), 2.60 (s, 6H, Ar-CH₃), 2.68 (s, 6H, thiophene-CH₃), 2.81 (s, 4H, N-CH₂thiophene), 3.80 (s, 4H, N-CH₂-Ph), 3.88 (s, 4H, N-CH₂-CH₂-N), 4.50 (d, J = 5.5 Hz, 4H, Ar-CH₂-OH), 7.01 (s, 2H, Ar-H), 7.05 (s, 2H, Ar-H), 7.45 (d, J = 3.8 Hz, 2H, thiophene-H), 7.62 (d, J = 3.8 Hz, 2H, thiophene-H),10.11 (br. s, 2H, Ar-OH). When one drop of D_2O was added to the ¹H NMR sample, the signals at 10.11 and 1.70 ppm disappeared, and the doublet at 4.50 ppm sharpened into a singlet at 4.49 ppm. The highresolution mass spectrum showed the main peak at m/z = 580.2435corresponding to the monopositively charged compound. Anal. calcd. for C₃₂H₄₀N₂O₄S₂: C, 66.17; H, 6.94; N, 4.82. Found: C, 66.48; H, 6.66; N, 4.51.

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