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NOTE

Synthesis of 6,6'-Diaminomethyl-*tris*-(pyridin-2-ylmethyl)amine

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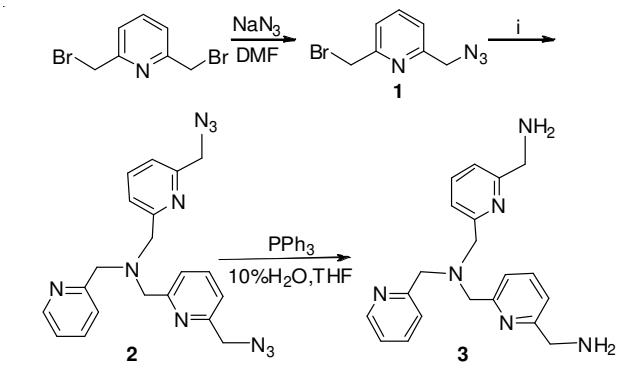
A new tripodal receptor 6,6'-diaminomethyl-*tris*-(pyridin-2-ylmethyl)amine was designed, synthesized and characterized by ^{1}H NMR, ^{13}C NMR and IR analysis.

Key Words: Receptor, Ligand, Synthesis, 2,2-Dipicolyamine.

Fluorescent sensor based on small organic molecule for recognition and quantitative analysis of metal ions is an active research in recent years[1-3] and become a powerful tool in chemistry, modern biology and environmental science, due to its high accuracy, selectivity, rapidity, ease of measurement, non-destructive methodology and direct visual perception[4-5]. A fluorescent sensor for metal ion generally contains a receptor (ligand: the recognition site) and a fluorophore (the signal source)[6]. The receptor binds to metal ion with a certain dissociation constant (K_d) and translates the recognition event into the fluorescence signal. To obtain a large spectroscopic response, the design and synthesis of efficient receptors must be carefully selected, which is an emergent field in supramolecular chemistry. Zn^{2+} and Cd^{2+} are two of metal ions of high concern by chemists and biologists and the development of receptors for Zn^{2+} and Cd^{2+} have aroused many scientists' interests. 2,2′-Dipicolylamine (DPA) is a well-known receptor and shows high selectivity[7-9] for Zn^{2+} and Cd^{2+} over Ca^{2+} and Mg^{2+} and many fluorescent receptors based 2,2′-dipicolylamine for Zn^{2+} or Cd^{2+} have been designed and led to great advances in their analysis. However, many of such receptors have disadvantages such as insufficient selectivity or sensitivity, or serious interference between Zn^{2+} and Cd^{2+}, which usually induced a comparable fluorescence response to Zn^{2+} and Cd^{2+}. In this sense, the design and synthesis of fluorescent receptor molecules for Zn^{2+} and Cd^{2+} would be highly valuable[10,11].

Accordingly, we designed a new flexible tripodal receptor **3** based 2,2′-dipicolylamine including three pyridine amine units and three alkyl amine units as recognition sites for Zn^{2+} or Cd^{2+}, which might be expected to obviously improve sensitivity and the selectivity especial for Zn^{2+} or Cd^{2+} with no interference to other multiple transition metal ions due to the effect of cooperative chelating.

The receptor **3** was prepared according to procedure given in **Scheme-I**. 2,6-*Bis*(bromomethyl)pyridine was first diazotized with NaN_3 to obtain compound **1**. Nucleophilic agent (2-pyridylmethyl)amine reacted with compound **1** to give compound **2** by S_N2 nucleophilic substitution and the two diazo groups of compound **2** were reduced with PPh_3 to produce primary amine groups by Staudinger reaction. The target compound **3** was obtained in satisfactory yield and characterized by ^{1}H and ^{13}C NMR and FT-IR.



(i) (2-pyridylmethyl)amine (0.5 equivalent), Et(*i*-Pr)$_2$N, CH_2Cl_2, RT, 3 days

Scheme-I: Synthesis of 6,6'-diaminomethyl-*tris*(2-pyridin-2-ylmethyl)amine

Silica gel (200-300 mesh, Qingdao) was used for column chromatography. 2,6-*Bis*(bromomethyl)pyridine and 2-(amino-

methyl)pyridine were purchased from HEOWNS Biochem Technologies LLC and used as received. Solvents for synthesis were of analytical grade or better and were dried. Fourier transform infrared (FTIR) spectra (4000-400 cm^{-1}) in KBr were recorded using a Bruker Vector 22 spectrometer. The NMR spectra were recorded on $CDCl_3$ solutions with tetramethyl silane (TMS) as an internal standard using Bruker AV-400 NMR spectrometer.

2,6-Monobromomethylazidomethypyridine (1): NaN_3 (0.065 g, 1 mmol) was added to a solution of 2,6-*bis*(bromomethyl)pyridine (0.892 g, 3.37 mmol) in dry N,N-dimethyl formamide (19.5 mL). The reaction mixture was stirred under atmosphere of argon for 5 days at room temperature. The solvent was removed *in vaccuo* and the residue suspended in CH_2Cl_2 (30 mL). The suspension was filtered through celite, dried with anhydrous Na_2SO_4. After cloumn chromatography on silica gel (200-300 mesh), eluting with CH_2Cl_2, a colourless oil was obtained (0.154 g, 68 % yield) and the starting material was recovered as white solid. ^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 4.51 (s, 2H, CH_2), 4.53 (s, 2H, CH_2), 7.27 (d, 1H, *J* = 8 Hz, ArH), 7.39 (d, 1H, *J* = 8 Hz, ArH), 7.73 (t, 1H, *J* = 7.8 Hz, ArH).

6,6'-Diazidomethyl-*tris*-(pyridin-2-ylmethyl)amine (2): A solution of compound **1** (0.179 g, 0.79 mmol), (2-pyridylmethyl)amine (0.041 mL, 0.39 mmol) and N,N-diisopropylethylamine (0.109 mL, 0.79 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 3 days under an argon atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to yield brown solid. The residue was dissolved in $CHCl_3$ and washed with saturated $NaHCO_3$ then brine solutions. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated from the filtrate under reduced pressure to give a light yellow oil (0.120 g, 78 % yield). TLC (CH_2Cl_2:MeOH = 25:1, v/v) R_f = 0.53. ^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 3.89 (s, 6H, $3CH_2$), 4.37 (s, 4H, $2CH_2$), 7.12-7.14 (m, 3H), 7.48 (d, 2H), 7.47-7.64 (m, 4H), 8.47 (d, 1H).

6,6'-Diaminomethyl-*tris*-(pyridin-2-ylmethyl)amine (3): Triphenylphosphine (0.188 g, 0.72 mmol) and water (0.15 mL) were added to a solution of compound **2** (0.120 g, 0.31 mmol) in tetrahydrofuran (3 mL). The resulting solution was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (8 mL) and CH_2Cl_2 (5 mL). The pH was adjusted to 1 using 2 M HCl and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2. The pH of the aqueous layer was adjusted to 10 using 2 M NaOH and extracted several times with CH_2Cl_2. The organic layer was concentrated under reduced pressure to a yellow oil (0.06 g, 56 % yield). ^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 2.67 (s, 4H, $2NH_2$), 3.89 (s, 6H, $3CH_2$), 3.93 (s, 4H, $2CH_2$), 7.00-7.10 (m, 3H, ArH), 7.33 (d, 2H, ArH), 7.49-7.60 (m, 4H, ArH), 8.47 (d, 1H, ArH). ^{13}C NMR (100 MHz, δ ppm, $CDCl_3$): 44.84, 60.16, 66.50, 122.06, 122.94, 128.51, 132.00, 136.50, 149.07, 158.74, 159.24.

Since 1996, 2,2′-dipicolylamine has been used as the most popular receptor for Zn^{2+} or Cd^{2+} sensors. Some 2,2′-dipicolylamine-based receptors for Zn^{2+} or Cd^{2+} were devised, such as N,N-di-(2-picolyl)ethyl-enediamine (DPEN), *tris*(2-pyridylmethyl)amine (TPA) and N,N,N'-*tris*(pyridine-2-ylmethyl)ethylenediamine (TRPEN). However, 2,2′-dipicolylamine can also strongly bind first row transition metal ions, Ag^+, Cd^{2+}, Hg^{2+} and Pb^{2+}. One possible approach is to impose the conformational restraint to the receptor of ions in sensors. In this study, compound **3** was designed as a fluorescent selective tripodal receptor for Zn^{2+} or Cd^{2+} by derivatization of the 2,2′-dipicolylamine moiety with a high binding constant (K) value without affecting the selectivity against other metal ions.

^{1}H NMR of compound **3** exhibited signals at 3.89, 3.93 ppm that were integrated for a total of 10 alkyl protons of the five methylene groups. In addition, signals were present at 7.00-7.10, 7.33, 7.49-7.60, 8.47 ppm for a total of 10 aromatic protons on the pyridine ring. The ^{13}C NMR spectrum of compound **3** showed signals at 44.84, 60.16, 66.50 ppm for aliphatic carbons of the methylene moieties. Acromatic carbons exhibited signals at the chemical shift range of 122.06-159.24 ppm.

IR (KBr, ν_{max}, cm^{-1}): 3447, 3387, 3059, 3008, 2920, 2833, 1676, 1588, 1573, 1260, 1151, 1115, 1078, 798, 758. The FTIR spectra showed a weak broad band at 3447 cm^{-1} and 3387 cm^{-1}, indicating the presence of free NH groups. The stretch vibration absorption of the aromatic aldimine (C=N) was at 1588 cm^{-1} and 1573 cm^{-1}. The characteristic peaks of aromatic C-H group were around 3059 cm^{-1} and 3008 cm^{-1}, aliphatic C-H group around 2920 cm^{-1} and 2833 cm^{-1}.

The design of tripodal scaffold as ion receptor maybe open a new venue for ion sensor development and the synthetic pathway of the receptor based 2,2′-dipicolylamine we have developed can be applied to the preparation of diverse derivatives of **3** as a wide variety of metal ion receptors.

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