NOTE

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

ZHEN-JUAN DUAN, ZI-QI ZHANG, XUE-JIAO GAO, CHUN-YUE MA and SHUO WANG*

Key Laboratory of Food Nutrition and Safety, Ministry of Education of China, College of Food Science and Biotechnology, Tianjin University of Science and Technology, Tianjin 300457, P.R. China

*Corresponding author: Fax: +86 22 60601332; Tel: +86 22 60601430; E-mail: duanzhenjuan@126.com

(Received: 31 January 2013;

Accepted: 28 November 2013)

AJC-14456

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

Key Words: Receptor, Ligand, Synthesis, 2,2'-Dipicolylamine.

Fluorescent sensor based on small organic molecule for recognition and quantitative analysis of metal ions is an active research in recent years¹⁻³ 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 perception⁴⁻⁵. 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 selectivity⁷⁻⁹ 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 $\text{S}_{\text{N}}2$ 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 ^1H and ^{13}C NMR and FT-IR.

(i) (2-pyridylmethyl)amine (0.5 equivalent), $\text{Et}(i\text{-Pr})_2\text{N}$, 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 ($4000\text{--}400\text{ cm}^{-1}$) in KBr were recorded using a Bruker Vector 22 spectrometer. The NMR spectra were recorded on CDCl_3 solutions with tetramethylsilane (TMS) as an internal standard using Bruker AV-400 NMR spectrometer.

2,6-Monobromomethylazidomethylpyridine (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-dimethylformamide (19.5 mL). The reaction mixture was stirred under atmosphere of argon for 5 days at room temperature. The solvent was removed *in vacuo* and the residue suspended in CH_2Cl_2 (30 mL). The suspension was filtered through celite, dried with anhydrous Na_2SO_4 . After column 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. ^1H NMR (400 MHz, δ ppm, CDCl_3): 4.51 (s, 2H, CH_2), 4.53 (s, 2H, CH_2), 7.27 (d, 1H, $J = 8\text{ Hz}$, ArH), 7.39 (d, 1H, $J = 8\text{ Hz}$, ArH), 7.73 (t, 1H, $J = 7.8\text{ Hz}$, 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 ($\text{CH}_2\text{Cl}_2\text{:MeOH} = 25\text{:}1$, v/v) $R_f = 0.53$. ^1H 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). ^1H 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.

^1H 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. Aromatic 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 ($\text{C}=\text{N}$) 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.

ACKNOWLEDGEMENTS

This work was supported by the National Science Foundation for Distinguished Young Scholars of China (Project No. 31225021) and the Ministry of Science and Technology of China (Project No. 2011BAK10B03) and the Program for Changjiang Scholars and Innovative Research Team in University (Project no. IRT1166) and the open foundation for laboratory of Tianjin University of Science and technology of China (Project No. 1314A307) and Tianjin Municipal High School Science and Technology Development Fund Program (Project No. 20130610).

REFERENCES

1. E. Kimura and T. Koike, *Chem. Soc. Rev.*, **27**, 179 (1998).
2. J.F. Zhang, Y. Zhou, J.Y. Yoon and J.S. Kim, *Chem. Soc. Rev.*, **40**, 3416 (2011).
3. Y. Jeong and J.Y. Yoon, *Inorg. Chim. Acta*, **381**, 2 (2012).
4. M. Dutta and D. Das, *TRAC-Trends Anal. Chem.*, **32**, 113 (2012).
5. R. Martinez-Manez and F. Sancenon, *Chem. Rev.*, **103**, 4419 (2003).
6. T. Terai and T. Nagano, *Curr. Opin. Chem. Biol.*, **12**, 515 (2008).
7. E.M. Nolan, J. Jaworski, K. Okamoto, Y. Hayashi, M. Sheng and S.J. Lippard, *J. Am. Chem. Soc.*, **127**, 16812 (2005).
8. K. Kiyose, H. Kojima, Y. Urano and T. Nagano, *J. Am. Chem. Soc.*, **128**, 6548 (2006).
9. B. Tang, H. Huang, K.H. Xu, L.L. Tong, G.W. Yang, X. Liu and L.G. An, *Chem. Commun.*, 3609 (2006).
10. J. Jia, X. Tang and Y.F. He, *Chin. J. Org. Chem.*, **32**, 1803 (2012).
11. Z. Q. Guo, G.H. Kim, I. Shin and J.Y. Yoon, *Biomaterials*, **33**, 7818 (2012).