Synthesis of a novel macrocyclic ligand containing bipyridine units

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The 6-hydroxymethyl-6′-tetrahydropyranyloxymethyl-2, 2′-bipyridine (2) was synthesized by the reaction of 6, 6′-dihydroxymethyl-2, 2′-bipyridine (1) with 3, 4-dihydropyran (DHP). 6-Tetrahydropyranyloxymethyl-6′-iodomethyl-2, 2′-bipyridine (5) was obtained from mesylate and iodizating reaction of compound 2. The coupling of 2 and 5 followed by hydrolysis gave bis(6′-hydroxymethyl-2,2′-bipyridine-6-methyl) ether (7). The macrocyclic ligand 8 was obtained by treating 7 and 6,6′-dibromomethyl-2,2′-bipyridine. The synthetic conditions of the intermediate 2 and macocyclic ligand 8 were discussed.

Keywords Azacrown ether, bipyridine derivative, macrocyclic ligand

Introduction

The pyridine as an important coordination unit for metal ions is frequently introduced into various ligands.[1-5] The 2,2′-bipyridine group (bipy) has been very extensively studied both for its rich coordination chemistry of metal ions[6-8] and for the auto-assemblage properties of its complexes.[9,10] These attractive features prompted the introduction of the bipy unit into macrocyclic ligand.[11-14] In particular the photoactivity of metal complexes of macrocyclic ligands containing bipy in electron and energy transfer processes has attracted more attention,[12,15] because the photoactivity will result in the development of systems performing photo-induced processes related to solar energy conversion.[12]

In this paper, we describe the syntheses of a novel macrocyclic ligand containing three 2,2′-bipyridine units. The synthetic conditions of intermediate **2** and macrocyclic ligand **8** were discussed. The synthetic route is outlined in Scheme 1.

Experimental

General

All solvents and reagents were commercial products of analytical grade. THF was dried over Na and distilled before use. DMF was dried over anhydrous $MgSO_4$. ^1H NMR spectra were recorded on Brucker Sy-200 MHz spectrometer and chemical shifts were given in ppm relative to TMS. Mass spectra and elemental analyses were performed at the Laboratoire de Spectrométrie de Masse and the Service Central de Microanalyse du CNRS, Institut de Chimie, Strasbourg, respectively.

6-Hydroxymethyl-6′-tetrahydropyranyl (THP) oxymethyl-2,2′-bipyridine (**2**) *and 6,6′-di(tetrahydropyranyloxymethyl)-2,2′-bipyridine* (**3**)

6,6′-Dihydroxymethyl-2,2′-bipyridine (**1**) (1.2 g, 5.55 mmol), excess of DHP (6 mL), CH_2Cl_2 (3 mL) and *p*-toluenesulfonic acid (8 mg, 0.046 mmol, as the catalyst) were stirred at 80℃ under argon. When all solid disappeared (about 2 h), the reaction was completed. After removal of the excess DHP by evaporation under reduced pressure, CH_2Cl_2 (100 mL) and saturated solution (25 mL) of sodium hydrogen carbonate were added to the residue. The organic layer was separated and the solvent was removed. The residue was purified by chromatography on Al_2O_3 with hexane/AcOEt

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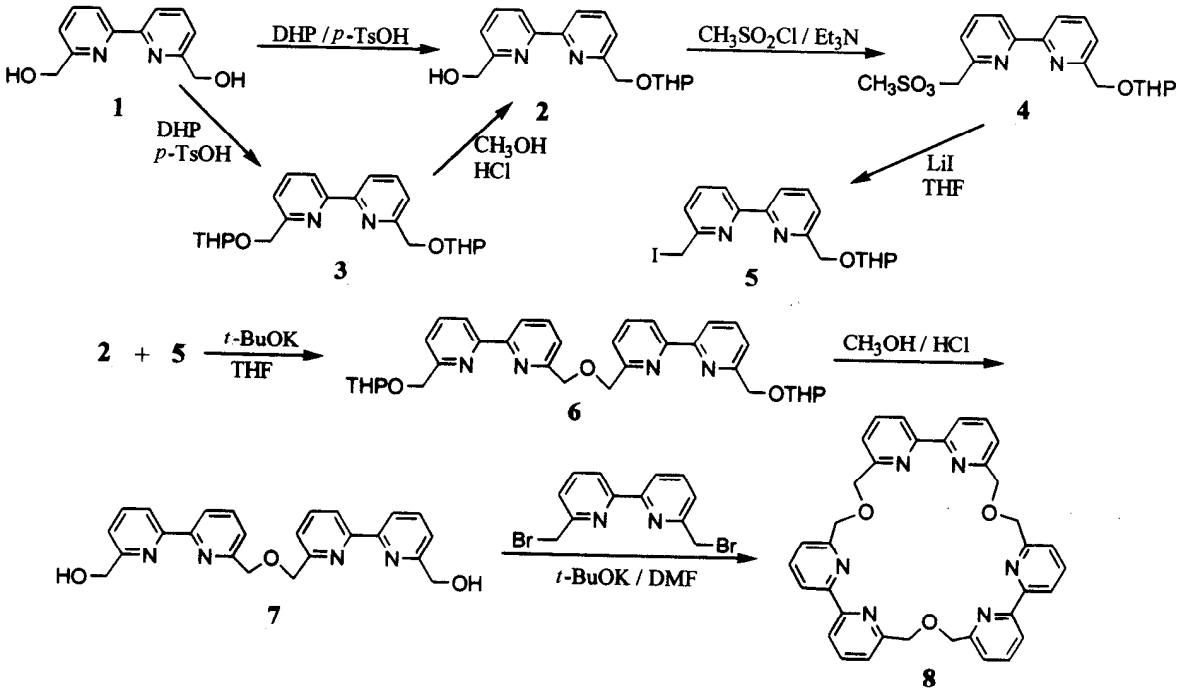
(V/V = 4:1, and then 1:1) as eluent, to give 0.55 g (33%) of **2** (pale yellow thick liquid) and 1.35 g (63%) of **3** (pale yellow thick liquid). Compound **2**, δ_H($CDCl_3$): 8.29(d, J = 7.80 Hz, 1H, 5-PyH), 8.24 (d, J = 7.82 Hz, 1H, 5'-PyH), 7.81 (t, J = 7.80 Hz, 1H, 4-PyH), 7.76 (t, J = 7.82 Hz, 1H, 4'-PyH), 7.47 (d, J = 7.80 Hz, 1H, 3-PyH), 7.18 (d, J = 7.82 Hz, 1H, 3'-PyH), 4.95 (d, J = 10.73 Hz, 1H, HCHOTHP), 4.80(t, J = 4.86 Hz, 3H, CH_2OH, THP-2-position H), 4.70(d, J = 10.73 Hz, 1H, HCHOTHP), 4.15(s, 1H, OH, after addition of D_2O, this peak disappeared), 3.50—4.00(m, 2H, THP-6-position H), 1.30—2.00(m, 6H, THP-3,4,5-position H). Anal. $C_{17}H_{20}N_2O_3$. Calcd: C,67.97; H, 6.72; N, 9.33. Found: C, 67.75; H, 6.82; N, 9.21. Compound **3**, δ_H($CDCl_3$): 8.25(d, J = 7.80 Hz, 2H, 5,5'-PyH), 7.85(t, J = 7.80 Hz, 2H, 4, 4'-PyH), 7.45(d, J = 7.80Hz, 2H, 3, 3'-PyH), 4.80(t, J = 4.88 Hz, 2H, THP-2-position H), 4.95 (d, J = 10.73 Hz, 2H, HCH), 4.70(d, J = 10.73 Hz, 2H, HCH), 3.30—4.10(m, 4H, THP-6-position H), 1.30—2.00 (m, 12H, THP-3,4,5-position H).

Scheme 1



The compound **2** was also obtained by methanolysis of **3** in the presence of a trace of HCl. A mixture containing **3** (1.35 g, 3.51 mmol), methanol (50 mL) and concentrated HCl (2 drops, about 0.1 mL) was stirred at 50℃ for 0.5 h under argon (the mol ratio of **3** versus HCl (37%) is about 3:1). After evaporation of the solvent, a saturated solution (50 mL) of $NaHCO_3$ was added and stirred for 10min. This mixture was extracted with $CHCl_3$(300 mL), and the combined extracts were concentrated till drying. The residue was purified by chromatography on Al_2O_3 with hexane/AcOEt (V/V = 4:1, and then 1:1) as eluent, to give 0.87 g (83%) of **2**. The total yield of **2** is 85—90%.

6-Tetrahydropyranyloxymethyl-6'-methanesulfonyloxymethyl-2,2'-bipyridine (**4**)

The compound **2** (0.87 g, 2.9 mmol), triethylamine (1.62 mL) and CH_2Cl_2 (15 mL) under argon were cooled in ice-bath and stirred, and then mesylchloride (0.46 mL, 5.9 mmol) was added at 0℃, white precipitate was produced after 5 min. The mixture was stirred for 0.5 h at room temperature and filtered on aluminium oxide (10 g), then the aluminium oxide was washed with hexane/AcOEt (1:1). The filtrate was concentrated under reduced pressure and the residue was dried in vacuum. The residue was purified by chromato-

graphy on Al_2O_3 with hexane/AcOEt (4:1, and then 1:1, *V/V*) as the eluent, to yield pure **4** (0.94 g, 85%, pale yellow stringy liquid). δ_H ($CDCl_3$): 8.40 (d, *J* = 7.80 Hz, 1H, 5-PyH), 8.30(d, *J* = 7.82 Hz, 1H, 5'-PyH), 7.85(t, *J* = 7.80 Hz, 1H, 4-PyH), 7.80(t, *J* = 7.82 Hz, 1H, 4'-PyH), 7.53(d, *J* = 7.80 Hz, 1H, 3-PyH), 7.48(d, *J* = 7.82 Hz, 1H, 3'-PyH), 4.95(d, *J* = 10.73 Hz, 1H, HC**H**OTHP), 4.80(t, *J* = 4.88 Hz, 1H, THP-2-position H), 4.75(d, *J* = 10.73 Hz, 1H, **H**CHOTHP), 3.50—4.00(m, 2H, THP-6-position H), 3.15(s, 2H, CH_2OS), 3.1(s, 3H, CH_3), 1.40—2.00(m, 6H, THP-3,4,5-position H). Anal. $C_{18}H_{22}N_2SO_5$. Calcd: C, 57.12; H, 5.87; N, 7.40. Found: C, 56.89; H, 6.01; N, 7.35.

6-Tetrahydropyranyloxymethyl-6'-iodomethyl-2,2'-bipyridine (**5**)

LiI (2.2 g, 16 mmol) was added at one time to the solution of **4** (1.06 g, 2.8 mmol) in THF (30 mL) with stirring under argon at room temperature. After stirring 20 min, the solvent was removed under reduced pressure, water (20 mL) and ether (120 mL) were added with stirring, the organic layer was separated and concentrated. The residue was purified by chromatography on Al_2O_3 with hexane/AcOEt (*V/V* = 3:2), to give pure **5** (0.75 g, 64%, pale brown thick liquid). δ_H ($CDCl_3$): 8.33(d, *J* = 7.80 Hz, 1H, 5-PyH), 8.25 (d, *J* = 7.82 Hz, 1H, 5'-PyH), 7.80(t, *J* = 7.80 Hz, 1H, 4-PyH), 7.70(t, *J* = 7.82 Hz, 1H, 4'-PyH), 7.47(d, *J* = 7.80 Hz, 1H,3-PyH), 7.37(d, *J* = 7.82 Hz, 1H, 3'-PyH), 4.95(d, *J* = 10.73 Hz, 1H, HC**H**O), 4.80(t, *J* = 4.86 Hz, 1H, THP-2-position H), 4.70(d, *J* = 10.73 Hz, 1H, **H**CHO), 4.60(s,2H,CH_2I),3.45—4.00(m,2H,THP-6-position H), 1.30—2.02(m, 6H, THP-3,4,5-position H). Anal. $C_{17}H_{19}IN_2O_2$. Calcd: C, 49.76; H, 4.68; N, 6.83. Found: C, 49.53; H, 4.71; N, 6.78.

Bis(6'-tetrahydropyranyloxymethyl-2,2'-bipyridine-6-methyl)-ether (**6**)

Potassium *t*-butoxide (0.41 g, 3.6 mmol) was added to the solution of **2** (0.53 g, 1.79 mmol) in THF (15 mL) at room temperature with stirring under argon. After stirring 10 min, a solution of **5** (0.735g, 1.79 mmol) in THF (15 mL) as added dropwise in about 0.5 h, and then the reaction mixture was stirred at 45℃ for 4 h. The solvent was removed under reduced pressure, water (20 mL) and $CHCl_3$ (150 mL) were added with stirring, the organic phase was separated and concentrated. The residue was purified by chromatography on Al_2O_3 with hexane/AcOEt (4:1), to give a pale yellow solid product **6** (0.56 g, 54%), mp 137—138℃. δ_H ($CDCl_3$): 8.37(d, *J* = 7.80 Hz, 2H, 5-PyH), 8.32 (d, *J* = 7.82 Hz, 2H, 5'-PyH), 7.87(t, *J* = 7.80 Hz, 2H, 4-PyH), 7.82(t, *J* = 7.82 Hz, 2H, 4'-PyH), 7.57(d, *J* = 7.80 Hz, 2H, 3-PyH), 7.50(d, *J* = 7.82 Hz, 2H, 3'-PyH), 4.95(d, *J* = 10.73 Hz, 2H, HC**H**OTHP), 4.90(s, 4H, CH_2OCH_2), 4.75(t, *J* = 4.86 Hz, 2H, THP-2-psition H), 4.72(d, *J* = 10.73 Hz, 2H, **H**CHOTHP), 3.52—4.15(m, 4H, THP-6-position H), 1.30—2.02(m, 12H, THP-3,4,5-position H). *m/z*(%): 583(M^+ + 1, 30). Anal. $C_{34}H_{38}N_4O_5$. Calcd: C, 70.07; H, 6.59; N, 9.62. Found: C, 69.85; H, 6.63; N, 9.58.

Bis(6'-hydroxymethyl-2,2'-bipyridine-6-methyl) ether (**7**)

A mixture containing **6** (0.23 g, 0.395 mmol), methanol (10 mL) and concentrated hydrochloric acid (5 drops) was stirred at 50℃ for 1.5 h under argon. After evaporation of the solvent, a saturated solution (20 mL) of $NaHCO_3$ was added and stirred for 10 min. This mixture was extracted with $CHCl_3$ (5 × 50 mL), and the combined extracts were concentrated till drying to afford a white solid which was recrystallized from $CHCl_3$ to furnish pure product **7** (0.15 g, 92%), mp 201—202℃. δ_H($CDCl_3$): 8.37(d, *J* = 7.89 Hz, 4H, 5,5'-PyH), 7.89(t, *J* = 7.89 Hz, 2H, 4-PyH), 7.79(t, *J* = 7.90Hz,2H,4'-PyH),7.58(d,*J* = 7.89Hz,2H, 3-PyH), 7.24(d, *J* = 7.90 Hz, 2H, 3'-PyH), 4.94 (s, 4H, C**H**$_2$OH), 4.84(s, 4H, CH_2OCH_2), 4.08 (s, 2H, OH, after addition of D_2O, this peak disappeared). *m/z*(%):415(M^+ + 1, 15). Anal. $C_{24}H_{22}N_4O_3$. Calcd: C, 69.54; H, 5.36; N, 13.52. Found: C, 69.36; H, 5.45; N, 13.42.

Macrocyclic ligand containing three bipyridine units (**8**)

DMF (50 mL) was placed in a 250 mL tetranecked flask equipped with a condenser with $CaCl_2$ dry-

ing tube, a thermometer and two constant pressure dropping funnels. A solution of **7** (40 mg, 0.096 mmol) and potassium t-butoxide(65 mg, 0.58 mmol) in DMF (50 mL), and a solution of 6,6′-dibromomethyl-2,2′-bipyridine (33 mg, 0.096 mmol) in DMF(50 mL) were added dropwise at the same time with vigorous stirring at 40℃ under argon in about 2 h. Then the mixture was allowed to react at 80℃ for 20 h, and the solvent was distilled off under reduced pressure to afford a pale brown solid. This solid was purified by chromatography on Al_2O_3 with CH_3OH/CH_2Cl_2 (1:99) to give a white solid product **8** (7 mg, 12.3%), mp 34—35℃. δ_H ($CDCl_3$): 7.98(d, J = 7.80 Hz, 6H, 5,5′-PyH), 7.63(t, J = 7.80 Hz, 6H, 4,4′-PyH), 7.44(d, J = 7.80 Hz, 6H, 3,3′-PyH), 4.85(s, 12H, CH_2). *m/z* (%): 595(M^+ + 1, 95). Anal. $C_{36}H_{30}N_6O_3$. Calcd: C, 72.70; H, 5.09; N, 14.13. Found: C, 72.48; H, 5.15; N, 14.01.

Results and discussion

6-Hydroxymethyl-6′-tetrahydropyranyloxymethyl-2,2′-bipyridine (**2**) was synthesized by the reaction of 6,6′-dihydroxymethyl-2,2′-bipyridine (**1**) and excess of DHP in the presence of a little *p*-toluene sulfonic acid as a catalyst at 80℃ for 2 h. Under otherwise equal conditions, when the mol ratio of **1** versus the catalyst is 65:1, the yield of **2** is 7%; or the reaction temperature is 90℃, the yield of **2** is 10%; or the reaction time is 2.5 h, compound **2** (17%) is obtained. It is necessary that the quantity of catalyst, the reaction temperature and the reaction time were controlled severely.

The compound **2** was also obtained by metholysis of **3** in the presence of a trace of HCl at 50℃ for 0.5 h, but the reaction conditions must be controlled severely. Under otherwise equal conditions, when the reaction temperature is 65℃, or the reaction time is 1.5h, or the mol ratioof **3** versus HCl (37%) is 1.5:1, only original material **1** is recovered.

The macrocyclic ligand **8** was synthesized by the reaction of intermediate **7** and 6,6′-dibromomethyl-2,2′-bipyridine with potassium *t*-butoxide as base and template. A large amount of white precipitate was produced in the reaction, this polymeric product can not be dissolved in any solvents. Because the diameter of potassium ion as a template is too small, which results in a large increase of the chain polymer and decrease the yeild of macrocyclic ligand.

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