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Synthesis of Novel Derivatives of Pyridine-2,6-dicarboxylic Acid

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Abstract: Two series of novel derivatives of pyridine-2,6-dicarboxylic acid with potential as polydentate ligands were synthesized from pyridine-2,6-dicarboxylic acid. All new compounds were characterized by NMR, MS, IR, and EA.

Keywords: Ligands, pyridine-2,6-dicarboxylic, synthesis

There has been steadily increasing interest in lanthanide coordination chemistry over the past two decades, essentially because of its potential applications in biology and medicine for analytical and diagnostic purposes such as time-resolved fluorescence immunoassay.[1,2] One challenge in the design of functional lanthanide-containing coordination compounds is the need for precise control of the Ln(III) inner coordination sphere, because a varying degree of nondirectional bonding is possible. Derivatives of pyridine-2,6-dicarboxylic acid, also known as dipicolic acid or DPA, are ubiquitous in biology[2] and have been found to be promising ligands in time-resolved fluorescence immunoassay. This is due to the stability of their lanthanide(III) complexes, and their strong fluorescence intensity with relatively long excitation lifetimes, which make the luminescent probe replaced radioimmunoassay (RIA). Much work has been devoted to designing polydentate ligands that can complex with lanthanide(III), resulting in luminescent complexes that can act as efficient light-conversion molecular devices (LCMDs).[3] These devices allow energy absorbed by the ligands to be transferred to the

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emitting metal ions, thus increasing the absorption UV cross section. Lamture et al. have designed a series of 4-substituted analogues of pyridine-2,6-dicarboxylic acid and noted that a 4-Cl substituent increases the energy transfer efficiency in DPA complexes of terbium(III).[4] However, there have been no reported syntheses of 4-hydroxyalkyl DPA derivatives, from which many multifunctional DPA derivatives could be prepared. In this article, we propose a simple strategy for introducing a hydroxymethyl group in the 4-position of DPA, thus opening way for the preparation of more elaborate ligands by substitution with nucleophiles containing strong coordinating groups, such as iminodiacetic acid.

Our synthetic strategy is outlined in Scheme 1. Esterification of DPA (**1**) with acidic methanol afforded DPA dimethyl ester **2**, which underwent direct nucleophilic aromatic substitution by a carbon-centered radical[5] to give the 4-hydroxymethylated derivative **3**[6] in moderate yield. The key intermediate **3** was converted to the corresponding iodide **5** under standard conditions, via the tosylate **4**, in good overall yield. Treatment of **5** with methyl acetoacetate under basic conditions gave the triester **6**, and similar reactions of **5** with dimethyl iminodiacetate and dimethyl malonate yielded the esters **8** and **10** respectively. Hydrolysis of the methyl esters **6**, **8**, and **10** afforded three novel DPA ligands, namely the acids **7**, **9**, and **11**. In addition, hydrolysis of 4-hydroxymetbyl DPA **3** gave the diacid **12**, and aminolysis of **3** afforded the novel diamide **13**.

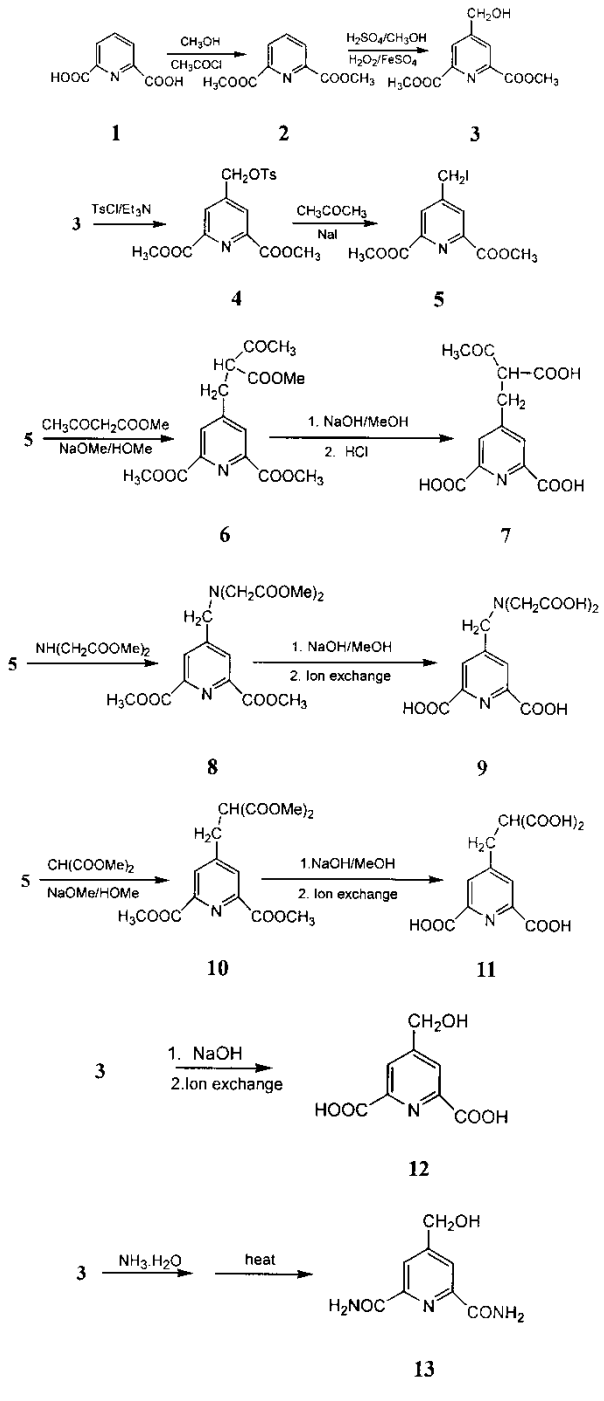
The amide functional group is found throughout nature in the primary structure of proteins and also plays an important role in coordination chemistry.[2] In this study, two polydentate pyridine diamide ligands were prepared by treating pyridine-2,6-dicarboxylic acid chloride (**15**) with pyrazole (**14**) and aminopyridine (**17**), as shown in Scheme 2. The resulting ligands **16** and **18** bear multiple N and O donor atoms in a large conjugated plane, which can protect metal ions from their environment when the complexes are formed, and in their fluorescence probe the shielding effect considerably reduces nonradiative deactivation processes.[7]

In summary, we have presented facile methods for the preparation of both 4-hydroxymethyl pyridine-2,6-dicarboxylic acid and polydentate pyridine-2,6-diamide derivatives of DPA from pyridine-2,6-dicarboxylic acid (**1**).

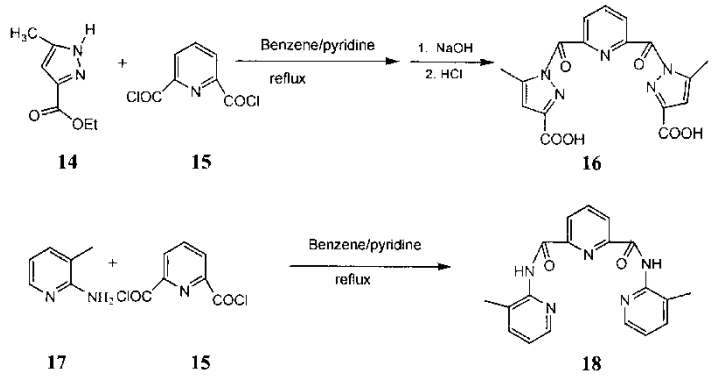
EXPERIMENTAL

General Information

IR spectra were measured on a Perkin-Elmer 1600 FT-IR spectrometer as KBr discs. MS was carried out on a HP-5988A GC-MS spectrometer. All nuclear magnetic resonance (NMR) spectra were recorded at 297 K with Varian 400-MHz spectrometer. Chemical shifts are reported as in ppm relative to TMS fixed at 0 ppm. Elemental analysis with C, H, N were



Scheme 1.



14 15 16

17 15 18

Scheme 2.

performed on a Perkin-Elmer 2400 elemental analyzer. Reactions were monitored by TLC, using precoated silica gel 60 F_{254} with detection under ultraviolet light.

The diester **2** was prepared according to Ref. 5, and the pyrazole **14** was prepared according to Ref. 7.

4-((bis(Carboxymethyl)imino)methyl)-pyridine-2,6-dicarboxylic Acid (9)

Solutions of $FeSO_4 \cdot 7H_2O$ (a saturated solution of 10 mL in water) and 30% H_2O_2 (70 mmol) were added dropwise to a vigorously stirred suspension of pyridine-2,6-dicarboxylic acid dimethyl ester (**2**) (1.95 g, 10 mmol) in methanol (10 mL) and 30% H_2SO_4 (10 mL), maintaining a reaction temperature of 15–30°C by control of the addition rate. The mixture was stirred for 10 min after the addition was complete, and K_2CO_3 was added to adjust the acidity of the solution to pH 6–7. After the solid was filtered off, the filtrate was extracted with ethyl acetate (5 × 20 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography eluting with 1 : 1 ethyl acetate–petroleum ether gave **3** as a colorless solid.

A solution of p-toluenesulphonyl chloride (6.88 g, 36.1 mmol) in CH_2Cl_2 (25 mL) at 0°C was added to 4-hydroxymethyl-pyridine-2,6-dicarboxylate **3** (5.81 g, 25.8 mmol) in CH_2Cl_2 (40 mL). After stirring at 0°C for 20 min, triethylamine (10 mL) was added dropwise in three portions at 20-min intervals. The mixture was stirred at 0°C for 15 min and at room temperature for a further 15 min. The reaction was diluted with ethyl acetate, and the organic phase was washed with water (3 × 20 mL) and 3% HCl (3 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallization from ether afforded the tosylate **4** as colorless needles.

The tosylate **4** (7.58 g, 20 mmol) was added to a solution of NaI (4.50 g, 30 mmol) in acetone (250 mL), and the reaction mixture was heated at reflux for 2.5 h. The cooled solution was diluted with ethyl acetate (550 mL), and the organic phase was washed with water (3 × 150 mL), 3% HCl (3 × 120 mL), and 5% Na_2SO_3 solution (2 × 50 mL). The organic extract was dried (Na_2SO_4) in darkness and concentrated under reduced pressure to give the crude iodide **5**.

$HN(CH_2COOMe)_2$ (0.58 g, 3.5 mmol) was added to a solution of the iodide **5** (0.60 g, 1.7 mmol) in THF (5 mL), and the mixture was stirred in darkness at room temperature for 12 h. The solvent was evaporated under reduced pressure, and the residue was washed with water (3 × 10 mL) and 5% $Na_2S_2O_3$ solution (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product, which was recrystallized from ethanol to afford the dimethyl ester **8** as a colorless solid.

A 30% NaOH solution (6 mL) was added to the diester **8** (1.8 g, 5.0 mmol) in methanol (50 mL), and the mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave a yellow solid, which was purified using a 732 cation resin column to give the diacid **9** as a colorless solid.

Diacids **7** and **11** were prepared from **6** and **8** using the same method as for **9**.

General Procedure for the Synthesis of Amide Derivatives of DPA

The amine **14** (3 mmol) and triethylamine (3 mmol) in anhydrous THF (20 mL) were added to a solution of 2,6-pyridinediformyl chloride **15** (1.5 mmol) in anhydrous THF (60 mL). The mixture was heated at reflux for about 6 h, when TLC indicated that the reaction was complete. After the suspension was cooled to room temperature, the precipitate was removed filtration and the filtrate was concentrated to about 8 mL. The resulting solid was filtered off to give the crude product, which was recrystallized from 1 : 1 $CHCl_3$–MeOH to give the diamide **16**.

The diamide **18** was similarly prepared from the acid chloride **15** and the pyrazole **17**.

Data

Compound 3.[6] Yield: 41%. Mp 154–158°C. IR (KBr): ν 3485, 3079, 3014, 2959, 1723, 1705, 1609, 1453, 1226, 1158, 984 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 2H, Py-3, 5-H), 4.91 (s, 2H, CH_2), 4.03 (s, 6H, OCH_3). m/z (FAB): 225 (M^+). Elemental analysis: calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.61; H, 4.92; N, 6.18.

Compound 4. Yield: 81%. Mp 136–137°C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 2H, Py-3, 5-H), 7.84–7.81 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.37–7.34

(d, $J = 8.2$ Hz, 2H, Ar-H), 5.16 (s, 2H, CH_2), 4.02 (s, 6H, OCH_3), 2.45 (s, 3H, Ar-CH_3). Elemental analysis: calcd. for $C_{17}H_{17}NO_7S$: C, 53.82; H, 4.52; N, 3.69. Found: C, 53.91; H, 4.52; N, 3.68.

Compound 5. Yield: 78%. Mp 148–150°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 2H, Py-3, 5-H), 4.45 (s, 2H, CH_2I), 4.04 (s, 6H, OCH_3). Elemental analysis: calcd. for $C_{10}H_{10}INO_4$: C, 35.84; H, 3.01; N, 4.18. Found: C, 35.88; H, 2.98; N, 4.15.

Compound 6. Yield: 61%. Mp 76–78°C. IR (KBr): ν 3428, 3081, 2962, 1742, 1723, 1611, 1566, 1450, 1367, 1158, 1001, 898 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 2H, Py-3, 5-H), 4.02 (s, 6H, OCH_3), 3.94 (t, $J = 7.2$ Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 3.30 (d, $J = 7.1$ Hz, 2H, CH_3), 2.27 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 168.5, 164.9, 150.6, 148.4, 128.4, 59.4, 53.2, 52.9, 32.6, 29.5. m/z (FAB): 324 ($M^+ + 1$). Elemental analysis: calcd. for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33. Found: C, 55.91; H, 4.32; N, 4.26.

Compound 7. Yield: 97%. Mp 187–189°C (decomp). ^{1}H NMR (400 MHz, D_2O): δ 8.03 (s, 2H, Py-3, 5-H), 3.84 (t, $J = 6.9$ Hz, 1H, CH), 3.68 (d, $J = 7.0$ Hz, 2H, CH_2), 2.33 (s, 3H, $COCH_3$). Elemental analysis: calcd. for $C_{12}H_{11}NO_7$: C, 51.25; H, 3.94; N, 4.98. Found: C, 51.32; H, 4.02; N, 4.94.

Compound 8. Yield: 95%. Mp 95–97°C. IR (KBr): ν 2996, 2958, 1746, 1732, 1720, 1439, 1417, 1214, 1162, 1014, 779, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H, Py-3, 5-H), 4.11 (s, 2H, CH_2), 4.03 (s, 6H, OCH_3), 3.72 [s, 6H, $(OCH_3)_2$], 3.58 (s, 4H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 165.2, 151.7, 148.6, 127.8, 56.6, 54.5, 53.2, 51.8. m/z (FAB): 368 (M^+), 337 (M-CH_3O), 309 (100%, M-CH_3O-CO), 209, 150. Elemental analysis: calcd. for $C_{16}H_{20}N_2O_8$: C, 52.17; H, 5.47; N, 7.61. Found: C, 52.32; H, 5.42; N, 7.84.

Compound 9. Yield: 98%. IR (KBr): 3461, 3131, 1724, 1710, 1637, 1604, 1560, 879, 726 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.50 (br s, 4H, COOH, exchange in D_2O), 8.29 (s, 2H, Py-3, 5-H), 4.04 (s, 2H, CH_2), 3.48 (s, 4H, $-NCH_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.1, 165.5, 152.4, 148.0, 126.9, 56.8, 54.1. Elemental analysis: calcd. for $C_{12}H_{12}N_2O_8$: C, 46.16; H, 3.87; N, 8.97. Found: C, 46.31; H, 3.92; N, 8.94.

Compound 10. Yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 2H, Py-3, 5-H), 4.16 (s, 6H, OCH_3), 3.87 (t, $J = 7.1$ Hz, 1H, CH), 3.61 (s, 6H, OCH_3), 3.09 (d, $J = 7.1$ Hz, 2H, CH_2). m/z (FAB): 340 ($M^+ + 1$), 308 (M-OCH_3), 281 (M-$COOCH_3 + 1$). Elemental analysis: calcd. for $C_{15}H_{17}NO_8$: C, 53.10; H, 5.05; N, 4.13. Found: C, 52.91; H, 5.06; N, 4.16.

Compound 11. Yield: 97%. ^{1}H NMR (400 MHz, D_2O): δ 8.15 (s, 2H, Py-3, 5-H), 3.68 (t, $J = 7.0$ Hz, 1H, CH), 3.47 (d, $J = 7.0$ Hz, 2H, CH_2). Elemental analysis: calcd. for $C_{11}H_9NO_8$: C, 46.65; H, 3.20; N, 4.95. Found: C, 46.31; H, 3.22; N, 4.98.

Compound 12. Yield: 100%. ^{1}H NMR (400 MHz, D_2O): δ 8.28 (s, 2H, Py-3, 5-H), 4.86 (s, 2H, CH_2). Elemental analysis: calcd. for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.10. Found: C, 48.59; H, 3.60; N, 7.13.

Compound 13. Yield: 98%. Mp 365–368°C. IR (KBr): ν 3423, 3313, 1698, 1666, 1602, 1404, 1335, 1063, 1114, 678 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (s, 2H, NH_2), 8.15 (s, 2H, Py-3, 5-H), 7.68 (s, 2H, NH_2), 5.62 (s, 1H, OH), 4.69 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 155.1, 148.9, 121.1, 61.4. Elemental analysis: calcd. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.22; H, 4.63; N, 21.87.

Compound 16. Yield: 32%. Mp 208–209°C. IR (KBr): ν 2901 (br COOH), 1700, 1698, 1671, 1666, 1573, 1557, 1521, 1450, 1367 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 2H, Py-3, 5-H), 8.11 (t, $J = 7.3$ Hz, 1H, Py-4-H), 6.31 (s, 2H, Pyraz.), 2.73 (d, 6H, CH_3) m/z (FAB): 383 (M^+). Elemental analysis: calcd. for $C_{17}H_{13}N_5O_6$: C, 53.27; H, 3.42; N, 18.27. Found: C, 53.72; H, 3.34; N, 18.34.

Compound 18.[8] Yield: 72%. Mp 120–123°C. IR (KBr): ν 3451, 3224, 1741, 1676, 1528, 1453, 1374 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, N–H), 8.70 (t, 1H, Py-4-H), 8.50 (s, 2H, Py-3, 5-H), 8.30 (2H, aminoPy-6′-H), 7.60 (2H, aminoPy-5′-H), 7.40 (2H, aminoPy-4′-H), 2.40 (s, 6H, CH_2) (should include 2 d.p. for the chemical shifts). ^{13}C NMR (100 MHz, $CDCl_3$): 161.8, 149.2, 146.1, 140.6, 139.6, 129.6, 122.4, 18.3. Elemental analysis: calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17; Found: C, 69.15; H, 5.31; N, 15.98.

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