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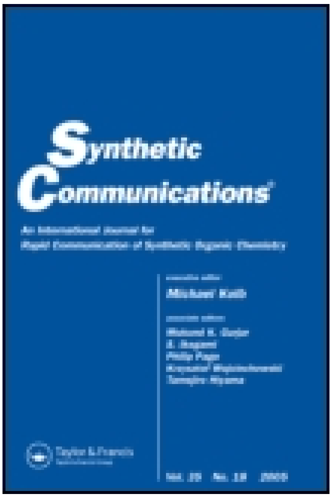

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Application of Wittig Reaction in Synthesis of Novel Pyridine Dicarboxylic Acid Derivatives with High Ligand Activity

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APPLICATION OF WITTIG REACTION IN SYNTHESIS OF NOVEL PYRIDINE DICARBOXYLIC ACID DERIVATIVES WITH HIGH LIGAND ACTIVITY

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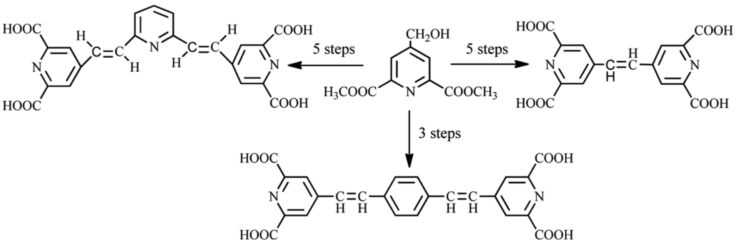
GRAPHICAL ABSTRACT



Abstract *A series of novel conjugated molecules with two pyridine dicarboxylic acid units have been synthesized by a Wittig reaction of corresponding alkyltriphenylphosphonium salts with aromatic aldehydes. The novel pyridine dicarboxylic acid derivatives with high ligand activity were completely characterized from their mass and* ^1H *NMR spectra. The E-configuration of these alkenes was confirmed by infrared spectroscopic data.*

Keywords Conjugated molecules; pyridine dicarboxylic acid; synthesis; Wittig reaction

INTRODUCTION

The Wittig reaction has been known for more than 50 years and is one of the most important carbon–carbon double-bond-forming reactions in organic chemistry.[1] It has attracted the attention of scientists worldwide because of its numerous applications in chemical sensing, asymmetric catalysis, material science, and large-scale reactions in industry.[2,3] The popularity of the Wittig reaction is mainly a result of the regioselective formation of the double bond at the position of the former carbonyl group and the possibility of controlling its stereoselectivity by applying special reaction conditions.[4]

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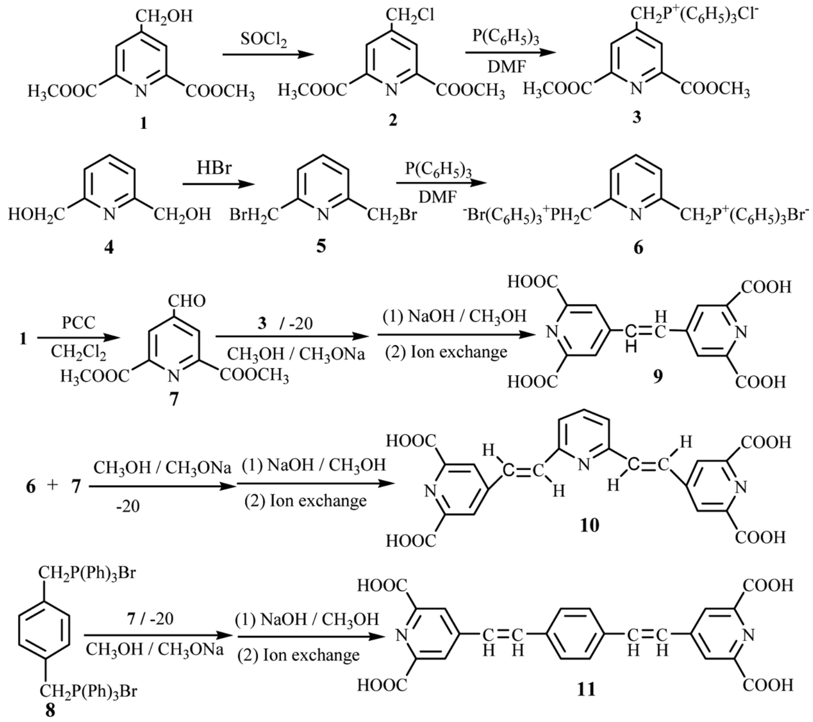

Scheme 1. The synthesis route.

Studies of fluorescent probes in biological media, optical amplification in fiber-optic telecommunications systems and photoluminescence devices are valuable.[5–8] To fully exploit the benefits of these interesting materials, there is a need for supramolecular systems with antenna units. Antenna molecules have one chromophore at one end of an array that can absorb a photon and the other chromophore at the opposite end of the array that will emit a photon subsequently. In recent years, some rare-earth complexes with β-diketon, aromatic carboxylic acid, and heterocyclic carboxylic acid group were under development, such as benzoyl acetone (BA),[9] benzoyltrifluoroacetone (BFA),[10] α-thenoyltrifluoroacetone (TTA),[11] and pyridine-2,6-dicarboxylic acid (DPA).[12] Since the lanthanide complexes with DPA derivatives are chiral, they can get more information about structure of biological molecules through measurement of circularly polarized luminescence spectra.[13,14] For this purpose, a few elegantly designed donor–acceptor pairs with one pyridine-2,6-dicarboxylic acid (DPA) compound have been synthesized and studied.[15] Our continuous interest in the synthesis of compounds led to the discovery of novel agents comprising two pyridine-2,6-dicarboxylic acid units because of their high absorption coefficient, strong donating ability, and good thermal, chemical, and photochemical stability.

Here we report the synthesis and characterization of a series of conjugated molecules in which two pyridine-2,6-dicarboxylic acid units are linked by a conjugated carbon–carbon double bond. The possibility that these compounds would be active stems from the fact that the previously described compounds have rigid conjugated planar structure, which would be beneficial to the electronic negotiability.[16] We report the detailed preparation for the compounds in Scheme 1.

RESULTS AND DISCUSSION

4-(Hydroxylmethyl)pyridine-2,6-dicarboxylate (compound **1**), p-xylylene bis-(triphenyl-phosphonium bromide) (compound **8**), and 2,6-bis(bromomethyl)pyridine (compound **5**) were synthesized as described in the literatures.[17–19]

The infrared (IR) spectra of compounds **9–11** display strong and sharp bands at 987–964 cm^{-1} and 1718–1738 cm^{-1} assigned to δ (=C-H) and ν (–C=O) stretching frequencies respectively, and the medium-intensity and wide bands at 1654–1635 cm^{-1} are attributed to ν(C=C), which suggests compounds **9–11** are *trans*-configuration with double bonds. The ^{1}H NMR spectrum displayed a singlet at δ 12.45–12.50, which accounts for the carboxyl proton; a multiplet appeared at δ 7.74–8.37, which accounts for five aromatic protons of the pyridine ring, multiplet appeared at δ 6.93–7.83 due to olefinic bond protons on the Py-CH=C and Ar-CH=C protons.

To examine the thermal stability of the three compounds, thermal gravimetric (TG) and differential thermal analyses (DTA) were carried out between 150 and 450 °C in the static atmosphere of air. The heating rate is 10 °C/min, and the TG-DTA curves show the weight loses as the temperature increases. The mass-loss stage of the three compounds in region of 290–350 °C is attributed to decomposition, which indicates that they may be large conjugated molecules and would be beneficial to the electronic negotiability. Also, the two pyridines rings can chelate with two lanthanide ions respectively to form a π-extended conjugated netted structure, which increases the fluorescence efficiency.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were determined on an XR-4 apparatus (thermometer uncorrected). Contents of carbon, hydrogen, and nitrogen were determined using an Elementar Vario EL elemental analyzer. IR spectra (4000–400 cm^{-1}) were recorded with samples as KBr pellets on a Nicolet Nexus 670 Fourier transform (FT)–IR spectrophotometer. ^{1}H NMR were measured with a Bruker 400-MHz nuclear magnetic resonance spectrometer with $CDCl_3$ or dimethylsulfoxide (DMSO) as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra were measured using a ZAB-HS analyzer.

Synthetic Procedure for Compounds

Compound 2. Sulfuryl dichloride (2.4 g, 20.0 mmol) was added dropwise to a solution of compound **1** (3.0 g, 13.3 mmol) in anhydrous $CHCl_3$ (25 mL) under a nitrogen atmosphere at −5 °C with continuous stirring for up to 40 min. Excess solvent was removed under reduced pressure, and the crude product was purified by recrystallization from ethanol to give the flaxen solid **2** (2.8 g) after drying in vacuum.

Compound 5. To a mixture of bromhydric in acetic acid (250 mL), 2.40 g (26.0 mmol) of pyridine-2,6-dimethanol (compound **4**) were added refluxed for 36 h, and then cooled to 0 °C. The solution was concentrated under reduced pressure, and a whitish solid was obtained. The white precipitate obtained by filtration then was dissolved in CH_2Cl_2 and washed with an aqueous solution of Na_2CO_3. The organic phases were dried over $MgSO_4$ and evaporated to be dried under vacuum. Compound **5** was obtained.

Compound 7. Pyridinium chlorochromate (PCC, 11.2 g, 75.0 mmol) was added to the solution of compound **1** (11.2 g, 50.0 mmol) in dry dichloromethane (50 mL) at room temperature. After stirring for 5 h, 50% solvent was removed and ethyl acetate (100 mL) was added. The reaction mixture was washed with water (80 mL), sodium bicarbonate (5%, 80 mL × 2), and saturated brine (100 mL) sequentially. The organic layer was separated, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude solid product was purified by recrystallization (ethyl acetate/chloroform, 3:1) to give compound **3** as acicular whitish solid (9.6 g).

Compounds 9–11. A solution of triphenylphosphine (3.4 g, 12.5 mmol) and compound **2** (2.5 g, 10.0 mmol) in dimethylformamide (DMF) (5 mL) was refluxed for 5 h and then cooled to room temperature. Anhydrous benzene (15 mL) was added to the solution and refluxed for 1 h. The reaction mixture was filtered to obtain the colorless solid **3** (3.5 g)**. A** solution of sodium methanolate (0.4 g, 6.0 mmol) in 20 mL absolute methanol was added dropwise to the absolute methanol (50 mL) solution of compound **3** (2.6 g, 5.0 mmol) and compound **4** (1.2 g, 5.0 mmol) stirred up to 1 h under a nitrogen atmosphere at −20 °C, and kept overnight with stirring at room temperature. The solution was concentrated under reduced pressure, and a whitish solid **5** was obtained by flash chromatography, eluting from ethyl acetate, petroleum ether and chloroform (1:1:1, v/v). A solution of NaOH (30%, 18.0 g) was added to 4-(4-(2-(2,6-bis(methoxycarbonyl)pyridine-4-yl)vinyl)styryl)pyridine-2,6-dicarboxylate (5.6 g, 10.0 mmol) in methanol (80 mL), and the mixture was stirred at room temperature for 30 h. Then the pH was adjusted to 1 with HCl (3 mol/L). The whitish solid **9** (2.9 g) was obtained.

Compounds **10** and **11** were obtained following the same procedure described as compound **9** starting from compound **6** and compound **8**.

Data

Compound 2. Yield: 86.0%; mp 168–170 °C. IR (KBr), ν /cm^{-1}: 3079, 2959, 2836, 1725, 1710, 1380, 1257, 1125, 798. MS, *m/z*: 243 (M^+), 213 ($M\text{-}OCH_3$, 62%), 184 ($M\text{-}OCH_3\text{-}CO$, 100%). ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.27 (s, 2H, Py-H), 4.45 (s, 2H, CH_2Cl), 4.06 (s, 6H, OCH_3). EA (calculated for $C_9H_{10}O_5N$): % C, 49.65 (49.18); H, 4.15 (4.23); N, 5.52 (5.37).

Compound 5. Yield: 53.20%; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.45 (s, 4H, CH2), 7.40 (d, 2H, ArH), 7.80 (t, 1H, ArH). MS, *m/z*: 265 (M^+). EA (calculated for $C_7H_7NBr_2$): % C, 32.03 (31.73); H 2.57 (2.66), N, 5.23 (5.29).

Compound 7. Yield: 86.0%, mp 152–154 °C; IR (KBr), ν/cm^{-1}: 3037, 2960, 2861, 1734, 1706, 1355, 1213, 978, 781. MS *m/z*: 165 ($M\text{-}OCH_3\text{-}CO$, 100%). ^1H

NMR (400 MHz, $CDCl_3$), δ (ppm): 10.02 (s, 1H, CHO), 6.64 (s, 2H, Py-H), 4.06 (s, 6H, OCH_3). EA (calculated for $C_9H_{10}O_5N$): % C, 53.65 (53.82), H 4.10 (4.06); N, 6.30 (6.28).

Compound 9. Yield: 98.4%; mp 286–288 °C. IR (KBr), ν/cm^{-1}: 3450, 2918, 1734, 1636, 1593, 1399, 1259, 981, 696. ^1H NMR (DMSO-d_6), δ (ppm): 12.50 (s, H, COOH), 8.05 (s, 2H, Py-H), 6.96 (d, H, $J = 17.0$ Hz, Py-CH=).

Compound 10. Yield: 98.4%; mp 288–290 °C. IR (KBr), ν/cm^{-1}: 3456, 2919, 1738, 1635, 1598, 1340, 1257, 987, 685. ^1H NMR (DMSO-d6), δ (ppm): 6.93 (d, 2H, =HC-Py-CH=), 7.10 (d, 2H, Py-CH=), 7.74 (s, 1H, Py-H), 7.92 (d, 2H, Py-H), 8.25 (s, H, Py-H), 12.47 (s, H, COOH).

Compound 11. Yield: 96.1%. mp > 300 °C. IR (KBr), ν/cm^{-1}: 3448, 2981, 1718, 1654, 1594, 1396, 1288, 964. ^1H NMR (400 MHz, DMSO-d_6), δ (ppm): 7.83 (ds, 2H, J = 17.02 Hz, Ar-CH=), 7.32 (d, 2H, J = 16.352 Hz, Py-CH=), 8.37 (s, 4H, Py-H), 7.68 (s, 4H, Ar-H).

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