Novel and Efficient Procedure for the Preparation of Two Pyridine Dicarboxylic Acid Derivatives

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Abstract: New strategies for the synthesis of two pyridine dicarboxylic acid derivatives namely; 4-(2-(2,6-dicarboxypyridin-4-yl)vinyl)pyridine-2,6-dicarboxylic acid and 2,6-bis(2-(2,6-dicarboxy-pyridin-4-yl)vinyl)pyridine have been described. New oxidant used is a good example of green chemistry technology and the synthesis procedure harvest a high-purity product at a high yield.

Keywords: Pyridine dicarboxylic acid derivatives, New oxidant, Green chemistry technology, Planar Structure.

Introduction

Our research group has recently been interested in synthesis of the pyridine dicarboxylic acid derivatives with rigid conjugated planar structure, which would be beneficial to the electronic negotiability¹, as many of them are useful in the field of fiber-optic telecommunications systems²⁻⁵ and time resolved fluoroimmunoassay (TR-FIA)⁶⁻⁷.

In recent years, increasing attention has been focused on organic reactions in which environmental pollution reduced and aqueous media used. To the best of our knowledge, the pyridine dicarboxylic acid derivatives have been reported only in our previous studies⁸ in which the PCC oxidant was used and produced the wastewater containing heavy metals. We report here the new synthesis routes, in which the oxidants sodium salt of 2-nitropropane and recycled $K_3Fe(CN)_6$ were used. The reusability of $K_3Fe(CN)_6$ make it more attractive than previous oxidant. The synthesis routes are detailed in Scheme 1.

Scheme 1

Experimental

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

The required intermediates named dimethyl 4-(hydroxymethyl)pyridine-2,6-dicarboxylate (**1**) and dimethyl pyridine-2,6-dicarboxylate (**5**) were prepared using reported procedures⁹.

Preparation of dimethyl 4-(chloromethyl)pyridine-2, 6-dicarboxylate (**2**)

To a solution of compound **1** (3.0 g, 13.3 mmol) in anhydrous CHCl_3 (25 mL), sulfuryl dichloride (2.4 g, 20.0 mmol) as added drop wise under nitrogen atmosphere at -5°C with continuous stirring for 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** (yield 2.8 g) after drying in vacuum.

Preparation of dimethyl 4-formylpyridine-2, 6-dicarboxylate (**3**)

Sodium (3.45 g, 0.15 mol) was added to absolute EtOH (250 mL) in batches under nitrogen atmosphere and continuous stirring to the sodium solid disappeared, then 2-nitropropane (14.00 g, 0.15 mol) was added and stirred for 30 min. The compound **2** (37.30 g, 0.15 mol) was added to the mixture solution and heated to reflux for 4 h. Excess solvent was removed under reduced pressure. The residue was extracted by dichloromethane, then the solvent was removed to give the flaxen solid **3** (yield 39.35 g) after drying in vacuum.

Preparation of dimethyl 4-(methylenetriphenylphosphoniumchloride)pyridine-2, 6-dicarboxylate (4)

A mixture of triphenylphosphine (6.8 g, 25.0 mmol), compound **2** (5.0 g, 20.0 mmol) and DMF (10 mL) was refluxed for 5 h. To the above solution, the anhydrous benzene (30 mL) was added and refluxed for 1 h. The reaction mixture was cooled to the room temperature and filtered to obtain the colorless solid **4** (yield 7.0 g).

Preparation of pyridine-2,6-dicarbohydrazide (6)

A mixture of compound **5** (19.50 g, 0.10 mol), ethanol (50 mL) and hydrazine hydrate (80%, 15.0 mL) was refluxed for 6 h. 80% solvent was removed and water (20 mL) was added. Then the reaction mixture was kept for 8 h at -10° C. The white crystalline product (yield 16.8 g) thus obtained was filtered, washed and dried.

Preparation of pyridine-2, 6-dicarbaldehyde (7)

To the mixture of compound **6** (9.80 g, 0.05 mol, ammonia aqueous solution; 25 mL) and water (250 mL), K₃Fe(CN)₆ aqueous solution (49.0 g, 0.05 mol, 150 mL) was added dropwise at low temperature. The reaction mixture was stirred for 4 h at room temperature, then extracted by dichloromethane and washed with 10% Na₂CO₃ aqueous solution. The solvent was removed to give the off-white crystalline product (yield 6.05 g) after drying in vacuum.

Preparation of 4-(2-(2,6-dicarboxypyridin-4-yl)vinyl)pyridine-2,6-dicarboxylic acid⁸ (8)

To the mixture of compound **4** (5.2 g, 10.0 mmol), compound **3** (2.4 g, 10.0 mmol) and the absolute methanol (100 mL), the methanol solution of sodium methanolate (0.8 g, 12.0 mmol, 40 mL) was added dropwise and stirred for 1 h under nitrogen atmosphere at -20° C and kept it overnight with stirring at room temperature. The solution was concentrated under reduced pressure and a whitish solid 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 into 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 compound **9** (yield 3.9 g) was obtained.

Preparation of 2, 6-bis(2- (2, 6 -dicarboxypyridin-4-yl) vinyl)pyridine (9)

Compound **9** was obtained following the same procedure described as compound **8**.

Results and Discussion*Characterization data*

Compound **2**: Yield: 86.0%; m.p.168~17 °C. IR (KBr), ν /cm⁻¹: 3079, 2959, 2836, 1725, 1710, 1380, 1257, 1125, 798. MS, m/z : 243 (M⁺), 213 (M-OCH₃, 62%), 184 (M-OCH₃-CO, 100%). ¹H NMR (400MHz, CDCl₃), δ (ppm): 8.27 (s, 2H, Py-H), 4.45 (s, 2H, CH₂Cl), 4.06 (s, 6H, OCH₃). EA (calculated for C₉H₁₀O₅N): %C 49.65 (49.18), H 4.15 (4.23), N 5.52 (5.37).

Compound **3**: Yield: 86.0%; m.p.152~154 °C; IR (KBr), ν /cm-1: 3037, 2960, 2861, 1734, 1706, 1355, 1213, 978, 781. MS m/z : 165 (M⁺). ¹H NMR (400 MHz, CDCl₃), δ (ppm): 10.02 (s, 1H, -CHO), 6.64 (s, 2H, Py-H), 4.06 (s, 6H, -OCH₃). EA (calculated for C₉H₁₀O₅N): % C 53.65 (53.82), H 4.10 (4.06), N 6.30 (6.28)

Compound **4**: ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.90 (s, 6H, -CH₃), 5.09 (s, 2H, -CH₂-), 4.06 (s, 2H, Py), 7.68 (s, 17H, Py-H and Ar-H).

Compound **6**: Yield: 87.3%; IR (KBr), ν/cm^{-1} : 3272, 3186, 1691, 989. MS m/z : 195 (M^+). ^1H NMR (400 MHz, CDCl_3), $\delta(\text{ppm})$: 2.12 (s, 4H, NH_2), 7.86 (s, 2H, NH), 8.60~8.83 (m, 3H, $-\text{C}_5\text{H}_3\text{N}-$). EA (calculated for $\text{C}_7\text{H}_9\text{O}_2\text{N}_5$): % C 43.02 (43.08), H 4.60 (4.65), N 35.99 (35.88)

Compound **7**: Yield: 84.6%; m.p.124~127 °C; IR (KBr), ν/cm^{-1} : 3083, 1720, 1692, 598. ^1H NMR (400 MHz, CDCl_3), $\delta(\text{ppm})$: 10.21 (s, 2H, -CHO), 8.21 (d, 2H, Py-H, $J=7.2$), 8.12 (t, 1H, Py-H, $J=7.5$).

Compound **8**: Yield: 88.4%; m.p.286~288 °C. IR (KBr), ν/cm^{-1} : 3450, 2918, 1734, 1636, 1593, 1399, 1259, 981, 696. ^1H NMR ($\text{DMSO}-d_6$), $\delta(\text{ppm})$: 12.50 (s, 4H, -COOH), 8.05 (s, 4H, Py-H), 6.96 (d, 2H, $J=17.0$ Hz, Py-CH=).

Compound **9**: Yield: 87.7%; m.p.288~290 °C. IR (KBr), ν/cm^{-1} : 3452, 2923, 1738, 1635, 1598, 1340, 1257, 986, 685. ^1H NMR ($\text{DMSO}-d_6$), $\delta(\text{ppm})$: 6.91 (d, 2H, =HC-Py-CH=), 7.13 (d, 2H, Py-CH=), 7.74~8.27 (s, 7H, Py-H), 12.45 (s, 4H, COOH).

Conclusion

In conclusion, we have developed a novel and efficient synthetic pathway for the preparation of two pyridine dicarboxylic acid derivatives in more than 87% excellent yield. Compared to the synthetic methods reported in previous literature, the novel method not only enhanced the yield, but also made the operating units easy workup. Moreover, the excellent recyclability of the oxidant system makes this procedure cleaner, which is a good example of green chemistry technology.

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