

## A Facile Stepwise Synthesis of New (Iso)nicotinoyl Spacers via Anisotropic OH $\cdots\pi$ Interaction

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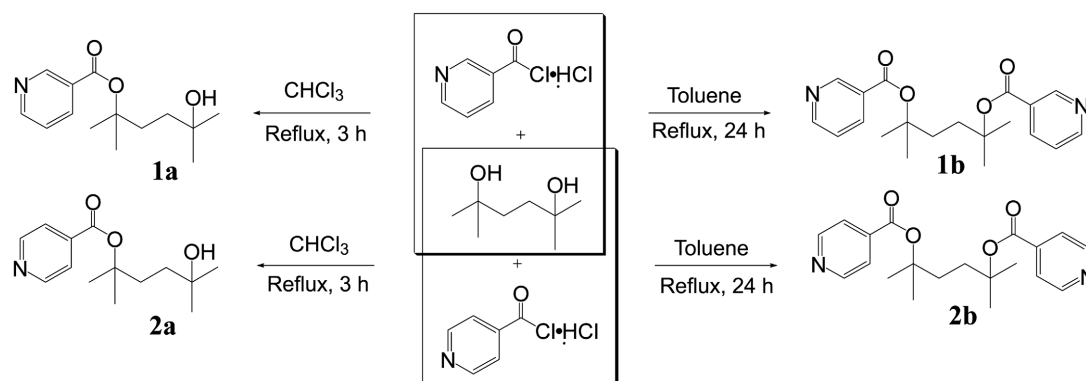
**Key Words :** N-Donor ligand, (Iso)nicotinoyl ligands, OH $\cdots\pi$  interaction, Stepwise reaction

Tuning of molecular topology of polypyridyl spacers *via* the balance of steric and inductive effects is an important field in supramolecular chemistry.<sup>1</sup> Such polypyridyl ligands that can bridge two or more remote metal centers have been utilized in the synthesis of abiotic functional supramolecules that exhibit mixed valence, anion exchange, photoinduced electron or energy transfer, sensing, polymorphism, and magnetic exchange between paramagnetic centers.<sup>2-12</sup> Thus, delicate design and synthesis of new tectonics is one of the most important tasks in the field of construction of functional supramolecular materials. In particular, isotropic and anisotropic weak hydrogen bonds as well as electronic and steric effects of substituted moieties play significant role in the synthesis of new spacer ligands.<sup>13</sup> Recently, among various polypyridyl tectonics, some (iso)nicotinoyl-containing spacers have served as appropriate building blocks for nanoscale supramolecular materials.<sup>14,15</sup> The (iso)nicotinoyl-containing spacers possess characteristic properties such as a potential multidentate, a  $sp^2$  angle around C=O ( $\sim 120^\circ$ ), a malleable length, conformational nonrigidity, and manageable solubility. In this context, we now describe a facile stepwise reaction of 2,5-dimethyl-2,5-hexanediol with (iso)nicotinoyl chloride *via* an anisotropic OH $\cdots\pi$  interaction.

The reaction of 2,5-dimethyl-2,5-hexanediol with (iso)nicotinoyl chloride progresses stepwise as shown in Scheme 1. Formations of the products are strongly dependent on the reaction temperature: the reaction in chloroform-reflux gives mono-substituted product whereas the reaction in toluene-reflux produces di-substituted

products. Their compositions and structures were confirmed by chemical analysis, IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR. Di-substituted products, **1b** and **2b**, were recrystallized in a mixture of chloroform and *n*-hexane (1 : 1) to obtain crystalline solids. Mono-isonicotinoyl product **2a** is obtained as crystalline solids, but mono-nicotinoyl analogue **1a** is obtained as viscous liquids. The products are soluble in common organic solvents such as acetone, chloroform, methanol, ethanol, dimethyl formamide, and dimethyl sulfoxide, but are insoluble in water. All products are stable even in solutions.

In order to examine the reason of the prominent stepwise reaction, energy minimizations of the mono-substituted compounds, **1a** and **2a**, were carried out by the empirical method (MM2) using the Chem3D Ultra 8.0 (Figure 1). As shown in the figure, the remaining OH group is covered with a perpendicular pyridyl group: perpendicular distance of OH $\cdots\pi$  is 1.98 Å for **1a** and 1.82 Å for **2a**. This is, the OH group is locked intramolecularly by a perpendicular pyridyl group, and thus further reaction of the mono-substituted does not occur at the reaction condition. The actual mono-substituted compounds should be pyridinium salts, **1a**·HCl and **2a**·HCl during the reaction, and thus, the stable conformations of the salt forms were calculated, resulting in the similar results as shown in Figure 1. However, the OH $\cdots\pi$  interaction of **2a**·HCl (1.97 Å) is slightly longer than that of **2a**, presumably owing to the deficient  $\pi$ -electron in the ring. If so, the further reaction should need the more vigorous condition to overcome 2-20 kJ/mol of such an OH $\cdots\pi$  interaction.<sup>13</sup> The similar reactions in toluene give

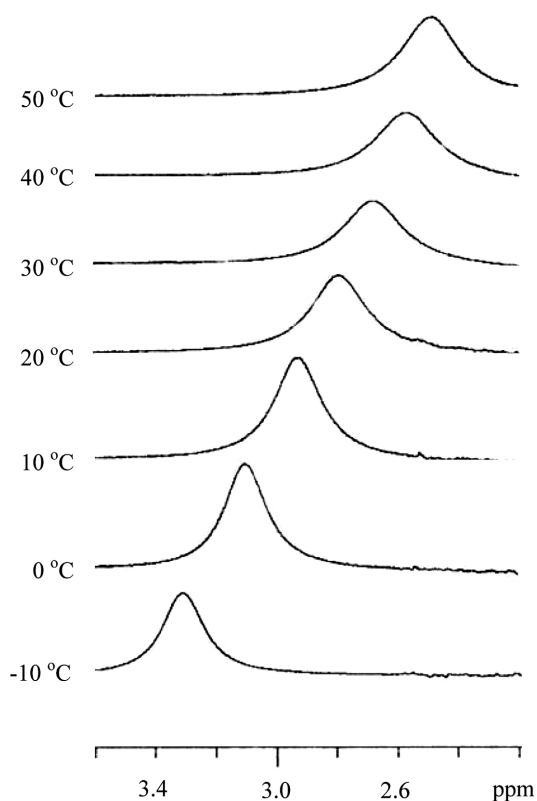


Scheme 1

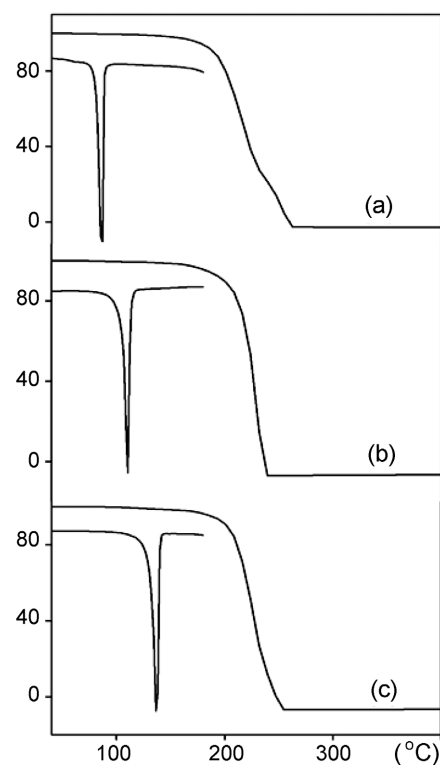


**Figure 1.** The most stable conformations of 2,5-dimethyl-2-hydroxy-5-isonicotinoylhexane (**2a**) (left) and **2a.HCl** (right) modeled from Chem3D Ultra (MM2), indicating the presence of OH $\cdots\pi$  interaction.

di-substituted products, **1b** and **2b**. For the further reaction, reaction time is also another important factor. For example, the reaction for 10 h yields about 40% product. The similar reaction pattern for both nicotinoyl and isonicotinoyl chloride suggests that the locked OH $\cdots\pi$  interaction is more rate-determinable rather than the N-position of pyridyl group. The N-position of pyridyl group, *i.e.* nicotinoyl chloride and isonicotinoyl chloride, is not a significant factor in this reaction condition, indicating that an OH $\cdots\pi$  interaction is more significant rather than an OH $\cdots$ N interaction. The  $^1\text{H}$  chemical shift of OH shields linearly with temperature-raising, indicating that the behavior of OH group is strongly dependent upon temperature (Figure 2). For **2a**, the similar behavior in solution is observed. Other



**Figure 2.** Temperature-dependent  $^1\text{H}$  NMR of OH group in **1a**.



**Figure 3.** Overlay of TGA and DSC curves of **2a** (a), **1b** (b), and **2b** (c).

chemical shifts of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the chemical structures. The thermal analyses have been used to establish a relationship between structure and properties.<sup>16</sup> To use the present compounds as tectonics for supramolecular materials, their thermal behaviors are important factor. Compounds, **1b** and **2b**, have a sharp melting point at 110 °C and 138 °C with each corresponding endothermic peak as shown in Figure 3. The high melting point of isonicotinoyl compound relative to the nicotinoyl analogue may be ascribed to the symmetry of isonicotinoyl moiety. **2a** is crystalline solids with 88 °C melting point whereas **1a** is viscous liquid at room temperature. All compounds decompose around 210 °C.

In conclusion, the symmetrical and unsymmetrical nicotinoyl containing spacers have been synthesized and characterized. In particular, the reaction is a prominent stepwise *via* an intramolecular anisotropic OH $\cdots\pi$  interaction. Preliminary experiments show that the spacer ligands are good tectonic for desirable supramolecular structures such as molecular boxes, cubes, and strands.

## Experimental Section

**Materials and Measurements.** Reagent grade 2,5-dimethyl-2,5-hexanediol and (iso)nicotinoyl chloride were used as received from Aldrich.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded on a Varian Gemini 300 instrument operating at 300.00 and 75.48 MHz, respectively. Variable temperature  $^1\text{H}$  NMR spectra were obtained by a Varian Gemini 500 instrument. The chemical shifts were relative to internal

Me<sub>4</sub>Si (<sup>1</sup>H and <sup>13</sup>C) for the indicated nuclei. The infrared spectra in the 5000-400 cm<sup>-1</sup> region were measured as alkaline metal halide pellets on a Perkin Elmer 16F PC model FT-IR spectrometer. Elemental analysis was performed at the Advanced Analysis Center at KBSI. Thermal analyses were carried out under dinitrogen atmosphere at a scan rate of 10 °C/min using a Stanton Red Croft TG 100. The molecular modeling was carried out by the empirical method using the Chem3D Ultra 8.0 (MM2).

**Preparation of 2,5-Dimethyl-2-hydroxy-5-nicotinoyl-hexane (1a).** 2,5-Dimethyl-2,5-hexanediol (1.83 g, 5.00 mmol) was added to a cold mixture of nicotinoyl chloride·HCl (4.90 g, 0.11 mmol) and pyridine (4.04 mL, 0.20 mol) in chloroform (150 mL) under nitrogen. The reaction mixture was stirred and refluxed for 3 h, and then was cooled and added into ice/H<sub>2</sub>O mixture. The chloroform layer was washed successively with 0.5 N NaOH solution and cold H<sub>2</sub>O. The chloroform solution was dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with ethyl acetate. Evaporation of solvent gave viscous liquid in 62% yield. Anal. Calcd for C<sub>14</sub>H<sub>21</sub>NO<sub>3</sub>: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.40; H, 8.32; N, 5.50. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 9.18 (s, 1H), 8.74 (d, *J* = 5 Hz, 1H), 8.22 (d, *J* = 4 Hz, 1H), 7.36 (m, 1H), 1.98 (t, *J* = 4 Hz, 2H), 1.56 (t, *J* = 4 Hz, 2H), 1.60 (s, 3H), 1.21 (s, 3H). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 164.22, 152.75, 150.57, 137.19, 127.79, 123.43, 84.32, 70.18, 37.79, 35.72, 29.33, 26.27. IR (KBr pellet, cm<sup>-1</sup>): 3407 (ν<sub>OH</sub>), 1716 (ν<sub>CO</sub>).

**Preparation of 2,5-Dimethyl-2,5-bis(nicotinoyl)hexane (1b).** 2,5-Dimethyl-2,5-hexanediol (1.83 g, 5 mmol) was added to a cold mixture of nicotinoyl chloride·HCl (4.90 g, 0.11 mmol) and pyridine (4.04 mL, 0.2 mol) in toluene (150 mL) under nitrogen. The reaction mixture was stirred and refluxed for 24 h, and then was cooled and added into ice-H<sub>2</sub>O mixture. The toluene layer was washed successively with 0.5 N NaOH solution and cold H<sub>2</sub>O. The toluene solution was dried (MgSO<sub>4</sub>) and the solvent was reduced under reduced pressure (20 mL). Excess hexane was added to the toluene solution, and left at 5 °C to obtain white solids in 84% yield. Mp. 110 °C. Anal. Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.30; H, 6.81; N, 7.77. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 9.19 (s, 1H), 8.67 (s, 1H), 8.22 (d, *J* = 4 Hz, 1H), 7.39 (m, 1H), 2.03 (s, 2H), 1.61 (s, 6H). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 164.27, 153.05, 150.83, 136.97, 127.61, 123.29, 83.86, 34.95, 26.25. IR (KBr pellet, cm<sup>-1</sup>): 1707 (ν<sub>CO</sub>).

**Preparation of 2,5-Dimethyl-2-hydroxy-5-isonicotinoyl-**

**hexane (2a).** The product was obtained as crystalline solids in 85% yield. Mp. 88 °C. Anal. Calcd for C<sub>14</sub>H<sub>21</sub>NO<sub>3</sub>: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.80; H, 8.36; N, 5.61. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 8.73 (s, 1H), 7.79 (d, *J* = 5 Hz, 1H), 8.22 (d, *J* = 4 Hz, 1H), 7.36 (m, 1H), 1.98 (t, *J* = 4 Hz, 2H), 1.57 (t, *J* = 4 Hz, 2H), 1.62 (s, 3H), 1.22 (s, 3H). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 164.10, 150.50, 139.27, 122.94, 84.62, 84.13, 70.58, 37.78, 35.60, 29.40, 26.20. IR (KBr pellet, cm<sup>-1</sup>): 3360 (ν<sub>OH</sub>), 1720 (ν<sub>CO</sub>).

**Preparation of 2,5-Dimethyl-2,5-bis(isonicotinoyl)-hexane (2b).** The product was obtained as crystalline solid in 85% yield. Mp. 138 °C. Anal. Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.20; H, 6.72; N, 7.59. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 8.75 (d, *J* = 4 Hz, 2H), 7.76 (d, *J* = 4 Hz, 2H), 2.02 (s, 2H), 1.62 (s, 6H). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ = 164.15, 150.65, 139.06, 122.91, 84.12, 34.83, 26.27. IR (KBr pellet, cm<sup>-1</sup>): 1717 (ν<sub>CO</sub>).

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