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# Synthesis of 2,6-di(1,8-naphthyridin-2-yl)pyridines functionalized at the 4-position: Building blocks for suitable metal complex-based dyes

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#### ABSTRACT

This study reports the synthesis of a methoxy-substituted 2,6-di(1,8-naphthyridin-2-yl)pyridine using Friedländer methodology. The functionalization at the 4-carbon of the methoxy-substituted derivative was confirmed by X-ray structural analysis. Finally, the methyl ether protecting group was cleaved to obtain 2,6-di(1,8-naphthyridin-2yl)pyridine-4-ol. Using the compounds, coordination behavior to ruthenium(II) center was also examined.

#### **GRAPHICAL ABSTRACT**



#### ARTICLE HISTORY

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#### **KEYWORDS**

Crystal structure; Friedländer condensation; naphthyridine; polypyridine; ruthenium complex

## Introduction

In recent years, environmental pollution and exhaustion of fossil fuels have become a serious problem, which have rendered the practical utilization of various renewable energy resources as a grand challenge in modern chemistry. Among these renewable energy resources, sunlight is considered the most useful resource. For example, dye-sensitized solar cells (DSSC), which are based on semiconductors such as  $TiO_2$ , have been studied as the next generation of solar cells.<sup>[1]</sup> The performance of DSSC is greatly affected by the molecular structure of the dye used.<sup>[2]</sup> This is exemplified by a variety of well-known ruthenium(II) complexes containing both thiocyanate ions (SCN<sup>-</sup>) and 2,2':6',2''-terpyridine derivatives (**1** in Fig. 1), which are typical polypyridine compounds.<sup>[3]</sup> Among these complexes, the SCN<sup>-</sup> ion, which functions as an electron acceptor site, is an ambidentate ligand, and therefore, it can bind to the Ru center with

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Figure 1. The structures of polypyridyl compounds containing the terpyridine skeleton.



Scheme 1. General synthetic procedure for synthesizing 1,8-naphthyridine derivatives (2) by the Friedländer reaction.

either a sulfur ( $\kappa S$ ) or a nitrogen atom ( $\kappa N$ ). Resultantly, the precise control of the coordination mode in such complexes is one of the key factors affecting their final performance because the resulting two linkage isomers often show different properties.<sup>[4]</sup>

We have reported that the coordination mode of the SCN ligand can be completely controlled using 2,6-di(1,8-naphthyridin-2-yl)pyridine (dnp; **2a** in Fig. 1), which is obtained by the condensation of two more pyridines to the terpyridine skeleton.<sup>[5]</sup> In addition, dnp and its derivatives have been shown to play an important role in electron transfer reactions because they are redox-active compounds.<sup>[6]</sup> The introduction of dnp in a dye molecule could be expected to improve the photoelectric conversion efficiency ( $\eta$ ) of DSSCs; however, the lack of a suitable anchor group in dnp for the adsorption on TiO<sub>2</sub> hinders its application as a dye. Generally, such anchor groups are phosphonates,<sup>[7]</sup> carboxylates,<sup>[8]</sup> or catechols,<sup>[9]</sup> whose oxygen atoms strongly adsorb on the surface of transition metal oxides. Although dnp derivatives containing a *t*-butyl substituent at the 4-position (**2b** in Fig. 1) have been reported,<sup>[10]</sup> no dnp skeleton molecules having the abovementioned anchor groups have been synthesized yet.

From the viewpoint of the importance of multifunctional dnp compounds, especially for their utilization as dye molecules, we herein describe our efforts toward the synthesis and characterization of dnp compounds containing oxygenated groups at the 4-position, as shown in Fig. 1 (2c and 2d). For the synthesis of 1,8-naphthyridine derivatives (2) such as dnp (Scheme 1), Friedländer condensation is the most commonly used method,<sup>[11]</sup> which involves the reaction between 2-aminonicotinaldehyde (3) and acyl derivatives (4). We applied this methodology to the proposed study using 4-methoxy-2,6-diacetylpyridine as the corresponding acyl derivative, which would provide a dnp derivative with a protected hydroxy group at the 4-position. As a preliminary study, we also examined the coordination chemistry between 2c and a ruthenium(II) center.

#### **Results and discussion**

First, we synthesized 2-aminonicotinaldehyde **3** through the known reaction of nicotinamide with ammonium amidosulfate.<sup>[11d,12]</sup> Aldehyde **3** must be freshly prepared and used immediately after isolation to avoid self-condensation side reactions. Meanwhile, the desired acyl precursor (**4**) must contain OR substituents, where R = alkyl or aryl, as protecting groups at the *para* position of the starting pyridine derivative. Since chelidamic acid has frequently been used as a starting material for the preparation of polypyridines,<sup>[13]</sup> and considering that it bears a functionality in the appropriate position, we selected chelidamic acid as the precursor for the synthesis of the desired 2,6-diacetylpyridine **4**.

The most convenient method for the preparation of 2,6-diacetylpyridine and its analogs is by conducting Claisen condensation of dialkyl pyridine-2,6-dicarboxylates and ethyl acetate in the presence of a strong base.<sup>[14]</sup> Therefore, we have tried to synthesize the desired 2,6-diacetylpyridine 4 according to the synthetic route.<sup>[14a,15]</sup> For the incorporation of the *para*-OMe substituent, chelidamic acid was first made to react with thionyl chloride and then with methanol to give a *para*-hydroxy methyl ester intermediate. After deprotonation and methylation with potassium carbonate and methyl iodide to avoid tautomerism between pyridine and pyridone, *para*-OMe methyl ester was obtained. The methyl ester was then converted to the *para*-OMe substituted diacetylpyridine 4 using standard methods.<sup>[16]</sup>

Next, the novel compound, 4-methoxy-2,6-di(1,8-naphthyridin-2-yl)pyridine (dnpOMe) 2c, was obtained by Friedländer condensation under a nitrogen atmosphere using aldehyde 3 and diacetylpyridine 4 (the first step in Scheme 2). The isolation yield (21%) of 2c after purification was lower than that obtained for its non-substituted counterpart (62% yield).<sup>[11f]</sup> This is most likely due to the difficulty in recrystallization rather than the difference in the reactivity of the respective acyl derivatives because of the low solubility of 2c in most organic solvents. The structure of dnpOMe 2c in solution was estimated from the corresponding <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data. Thus, the <sup>1</sup>H NMR spectrum of 2c showed a singlet corresponding to three protons at  $\delta = 4.13$  ppm as well as signals specific to dnp in the aromatic region.<sup>[11f]</sup> The proton-decoupled <sup>13</sup>C NMR spectrum of 2c showed 11 distinct resonances, which are consistent with the proposed structure. Additionally, the methoxy carbon resonated at  $\delta = 55.93$  ppm. Meanwhile, the percentage of C, H, and N in the bulk sample of 2c was determined by microanalysis, and it was in agreement with the calculated values.



Scheme 2. Synthesis of 4-substituted-2,6-di(1,8-naphthyridin-2-yl)pyridines 2c and 2d.



**Figure 2.** X-ray crystallographic structure of **2c** (CCDC: 1869682) with atom labels and displacement ellipsoids for non-hydrogen atoms drawn at the 50% probability level. The asymmetric unit of the crystal contains two chemically identical molecules, of which only one is shown. Hydrogen atoms are shown as small spheres of arbitrary radius.

Furthermore, the structure of 2c was confirmed by single-crystal X-ray crystallography (Fig. 2 and Supplementary Material). Compound 2c contains two molecules in the asymmetric unit, but both structures are chemically identical. All hydrogen atoms attached to the carbon atoms are clearly visible in the difference map, and the assignment of nitrogen atoms in aromatic rings is unambiguous. The central pyridine N atom exists in a *trans* conformation with respect to the naphthyridine N atoms. It was found that the OMe group in compound 2c was bonded to the 4-carbon atom, and the bond lengths and angles were within normal ranges.<sup>[17]</sup> Moreover, 2c contains some C-H...N hydrogen bonds and intermolecular  $\pi \dots \pi$  interactions (Supplementary Material). Due to these effects, the two aromatic groups tend to be coplanar.<sup>[18]</sup>

Subsequently, conversion of 2c to 2,6-di(1,8-naphthyridin-2-yl)pyridine-4-ol (dnpOH) 2d was conducted by deprotection using pyridine and hydrochloric acid at a reflux temperature of 220 °C (the second step in Scheme 2).<sup>[13]</sup> This deprotection reaction proceeded smoothly with high yield (85%). For both <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 2d, the signals derived from the OMe group ( $\delta$ =4.13 and 55.93 ppm, respectively) completely disappeared, which indicated the progress of the deprotection reaction. Additionally, the dnpOH 2d signal pattern indicates that 2d retains the dnp framework. Unfortunately, in the case of compound 2d, insufficient material was available for microanalysis because its weight increased accompanied by deliquescence when exposed to air. Nevertheless, the composition suggested by the corresponding HRMS data in solution supported the proposed structure. It is worth mentioning that we also attempted the deprotection of 2c using hydrobromic acid.<sup>[19]</sup> Although spectroscopic monitoring suggested a satisfactory outcome of this reaction, the isolation of 2d proved

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Scheme 3. Formation of a Ru-complex containing 2c.

to be extremely difficult. Therefore, we confirmed that the deprotection using pyridine and hydrochloric acid was superior in this system.

An attempt to prepare a family of ruthenium complexes containing 2 was successful.  $[Ru(dmso)_4Cl_2]$  (dmso = dimethyl sulfoxide)<sup>[20]</sup> was adopted as the precursor for the preparation of ruthenium(II) complexes having tridentate polypyridines such as dnp.<sup>[21]</sup> Actually, the aqua complex ( $[Ru(2c)(py)_2(OH_2)]^{2+}$ ) was directly synthesized without the formation of the corresponding chlorido complex (Scheme 3). Two naphthyridine units promote hydration both by electronic repulsion of the chloride leaving group and stabilization of the entering water through hydrogen bonds.<sup>[21]</sup> The complex was characterized by ESI-MS, <sup>1</sup>H NMR, and microanalysis. In <sup>1</sup>H NMR spectrum, a signal observed at 9.2 ppm disappeared upon the addition of  $D_2O_2$ , identifying it as the protons on the (Supplementary Material). Furthermore, a preliminary X-ray anacoordinated water lysis was performed to obtain structural information of the complex. Although the quality of the crystals of the complex was not good enough for a detailed analysis of the bond parameters, the ligand environment around the ruthenium atom was identical to the related complex with dnp (Supplementary Material).<sup>[21]</sup> Currently, the effort is being made to synthesize/characterize a series of ruthenium complexes with 2c or 2d and to explore their application to the photosensitizer. These results will be reported in subsequent papers.

### Conclusions

We have synthesized two kinds of functionalized dnp compounds, 2c and 2d, through Friedländer condensation reaction, providing access to the desired dnp skeleton containing a hydroxy group at the 4-position. Also, we have demonstrated the one-pot formation of the ruthenium complex containing 2c as a ligand. Considering the fact that the dye performance improves with an increase in the symmetry of the constituent molecule,<sup>[22]</sup> it can be expected that compound 2d could be suitable as a dye molecule from a structural viewpoint. Therefore, we hope that this compound will create new research pathways for effective dye molecules in DSSC applications.

#### Experimental

All chemicals were used without further purification. All solvents used for synthesis were anhydrous and used without further purification. Nicotinamide, ammonium amidosulfate, and chelidamic acid were purchased from Nacalai Tesque and Tokyo Chemical Industry, respectively. The compounds 2-aminonicotinaldehyde **3**, 4-metohxy2,6-diacetylpyridine 4, and  $[Ru(dmso)_4Cl_2]$  were prepared according to previously reported procedures.<sup>[11d,12a,12b,14a,15,20]</sup>

Microanalysis data were obtained on a Perkin Elmer 2400II series CHN analyzer. Melting points were determined on a Barnstead International 1201 D instrument. <sup>1</sup>H and <sup>13</sup>C {<sup>1</sup>H} NMR spectra were recorded on a JEOL JMN-AL300 spectrometer ( $25 \,^{\circ}$ C) operating at <sup>1</sup>H and <sup>13</sup>C frequencies of 300 and 75 MHz, respectively. Both spectra were referenced to external tetramethylsilane via residual protons of the solvent (<sup>1</sup>H) or the solvent itself (<sup>13</sup>C). Electrospray ionization mass spectrometry (ESI-MS) data were obtained on a Bruker Daltonics microTOF. High-resolution mass spectrometry (HRMS) data were obtained on a JEOL JMS-T100GC spectrometer.

## Synthesis of 4-methoxy-2,6-di(1,8-naphthyridin-2-yl)pyridine (2c)

A freshly prepared 2-aminonicotinaldehyde **3** (0.89 g, 7.3 mmol) and 4-methoxy-2,6-diacetylpyridine **4** (0.64 g, 3.3 mmol) were added to ethanol (30 mL). After addition of a freshly prepared ethanolic KOH solution (0.1 g/15 mL), the mixture was refluxed for 5 h under nitrogen. The solution was cooled to room temperature and then was allowed to stand at 4 °C overnight. The resultant yellow precipitate was collected by filtration, washed with diethyl ether, and then dried in vacuo. The crude product was recrystallized from methanol. Yield: 249 mg (21%); Colorless powder; mp 265–268 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 4.13 (s, 3H, -OC*H*<sub>3</sub>), 7.69 (dd, 2H, 6'-H, *J* = 8.1, 3.9 Hz), 8.31 (s, 2H, 3 and 5-H), 8.57 (dd, 2H, 5'-H, *J* = 8.1, 1.8 Hz), 8.71 (d, 2H, 4'-H, *J* = 8.4 Hz), 9.00 (d, 2H, 3'-H, *J* = 8.7 Hz), 9.16 (dd, 2H, 7'-H, *J* = 3.9, 1.8 Hz). <sup>13</sup>C {<sup>1</sup>H} NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 55.93 (-OCH<sub>3</sub>), 108.27, 119.79, 122.78, 123.02, 137.52, 139.01, 154.22, 155.10, 156.46, 157.68, 167.60. Anal. Calcd. for C<sub>22</sub>H<sub>15</sub>N<sub>5</sub>O·H<sub>2</sub>O: C, 68.92; H, 4.47; N, 18.27. Found: C, 68.77; H, 4.68; and N, 18.14.

## Synthesis of 2,6-di(1,8-naphthyridin-2-yl)pyridin-4-ol (2d)

4-Methoxy-2,6-di(1,8-naphthyridin-2-yl)pyridine **2c** (190 mg, 0.52 mmol) was dissolved in pyridine (14 mL). A concentrated HCl solution (12 M, 15 mL) was slowly added to the solution at 0 °C. The reaction temperature was slowly increased to 220 °C, after which time the mixture was refluxed for 3.5 h. Addition of water (50 mL) to the solution resulted in the formation of a white precipitate of **2d**. The product was collected by filtration, washed with cold water, and dried in vacuo. Yield: 155 mg (85%); Colorless solid; mp 336–340 °C (dec.). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 7.68 (dd, 2H, 6'-H, *J*=8.1, 3.9 Hz), 8.20 (s, 2H, 3 and 5-H), 8.56 (dd, 2H, 5'-H, *J*=7.8, 2.1 Hz), 8.69 (d, 2H, 4'-H, *J*=9.0 Hz), 8.98 (d, 2H, 3'-H, *J*=8.4 Hz), 9.15 (dd, 2H, 7'-H, *J*=4.2, 2.1 Hz). <sup>13</sup>C {<sup>1</sup>H} NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 110.33, 120.16, 122.78, 123.14, 138.76, 139.04, 153.48, 154.10, 156.00, 158.30, 166.38. HRMS (EI): *m*/*z* [M]<sup>+</sup> calcd for C<sub>21</sub>H<sub>13</sub>N<sub>5</sub>O 351.1120; found: 351.1110.

# Synthesis of $[Ru(dnpOMe-\kappa^3N)(py)_2(OH_2)](PF_6)_2$

[Ru(dmso)<sub>4</sub>Cl<sub>2</sub>] (117 mg, 0.24 mmol) and **2c** (86 mg, 0.24 mmol) were dissolved in ethylene glycol (6 mL) under N<sub>2</sub>, and the mixture was refluxed for 10 min. On cooling, Et<sub>3</sub>N (0.2 mL), EtOH (10 mL), H<sub>2</sub>O (6 mL), and pyridine (0.6 mL, 7.5 mmol) were added to the solution. The solution was refluxed for a further 26 h. The mixture was allowed to cool, and the aqueous solution was extracted with three 80 mL portions of dichloromethane. Blue powders precipitated when a saturated aqueous solution of KPF<sub>6</sub> was added to the mixture and allowed to cool overnight. The precipitate was collected by filtration, washed with cold water and diethyl ether, and then dried in vacuo. The crude product was purified by column chromatography on Al<sub>2</sub>O<sub>3</sub> (eluent: acetone). Yield: 40 mg (21%); Blue powder. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>):  $\delta$  = 4.33 (s, 3H, -OCH<sub>3</sub>), 7.00 (t, 4H, *J* = 7.2 Hz), 7.57 (t, 2H, *J* = 7.8 Hz), 8.07 (dd, 2H, *J* = 8.4, 4.5 Hz), 8.16 (dd, 4H, *J* = 6.6, 1.5 Hz), 8.83–8.86 (m, 4H), 8.97 (d, 2H, *J* = 8.4 Hz), 9.07 (d, 2H, *J* = 8.7 Hz), 9.23 (br, 1H, OH<sub>2</sub>), 9.48 (dd, 2H, *J* = 4.2, 2.4 Hz). MS (ESI): *m/z* 321.5 ([M]<sup>2+</sup>), 312.5 ([M-OH<sub>2</sub>]<sup>2+</sup>). Anal. Calcd. for C<sub>32</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub>F<sub>12</sub>P<sub>2</sub>Ru: C, 41.21; H, 2.92; N, 10.51. Found: C, 40.99; H, 2.67; and N, 10.27.

Supporting information <sup>1</sup>H and <sup>13</sup>C NMR spectra and X-ray crystallographic data. This material can be found via the "Supplementary Content" section of this article's webpage.

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