

THE AERIAL OXIDATION OF A COBALT(II)-2-AMINOMETHYLPYRIDINE COMPLEX: AN IMPROVED METHOD FOR SYNTHESIS OF 2,3,5,6-(TETRAPYRIDIN-2-YL) PYRAZINE

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Abstract – An excellent tridentate chelate compound for iron(II) ion, 2,3,5,6-(tetrapyridin-2-yl)pyrazine (**2**), was directly synthesized by aerial oxidation of a cobalt(II)-2-aminomethylpyridine complex. Oxidation pathways are also proposed.

The work of oxygen fixation by metal complexes has been contributed not only to unraveling the biological problem but also to an understanding of the pathways by which molecular oxygen functions as an oxidizing agent. The reversible complexation of molecular oxygen by cobalt(II)-ammine complexes had already been known in the nineteenth century.¹ Since the original

discovery of the oxygen-carrying properties of bis(salicylaldehyde ethyleneimine)-Co(II) complex,² a wide variety of analogous oxygen complexes have been characterized, generally as μ -peroxo complexes.³ In the course of studying tridentate chelate compounds, Lions and his co-worker⁴ found that 2,3,5,6-(tetrapyridin-2-yl)pyrazine (**2**) was an excellent tridentate for iron(II) cations wherein the compound (**2**) was synthesized by fusion of α -pyridoin and ammonium acetate in 32% yield. In a previous communication,⁵ we reported a new facile synthesis of **2** from 2-aminomethylpyridine (**1**) using cobalt(II) chloride. The reaction is based on the fixation of molecular oxygen by a cobalt(II) complex and just carried out in water or ethanol, although a trace amount of by-product, 2,4,5-(tripyridin-2-yl)oxazole (**3**), was formed (Scheme 1). This paper is concerned with an improved method for synthesizing the tridentate (**2**) and the investigation of the oxidation of **1** by molecular oxygen as an oxidizing agent.

Scheme 1

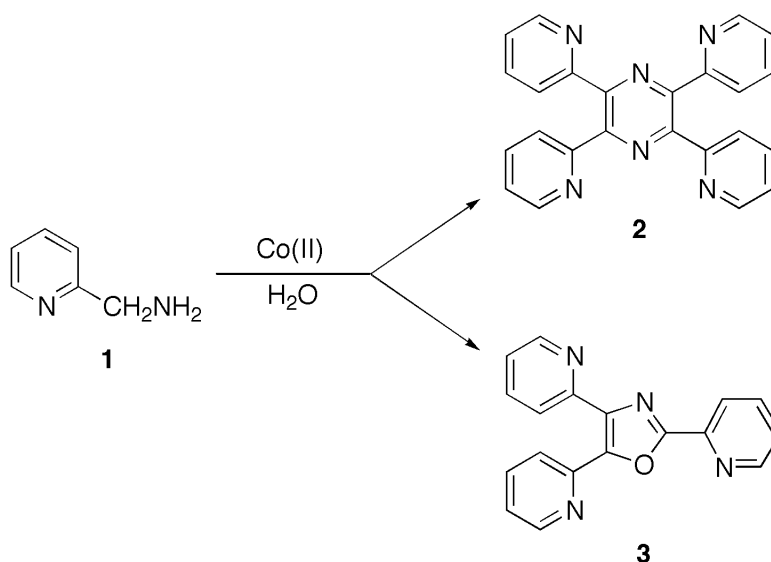


Table I

The Correlation between the molar ratio of **1** (1 g) to Co(II) ion and the yield of **2**^{*}

Entry	Molar ratio (1/Co(II)ion)	Yield(%) of 2
1	6 / 1	7.8
2	3 / 1	48
3	1 / 1	0.45

* Synthesized by procedure B

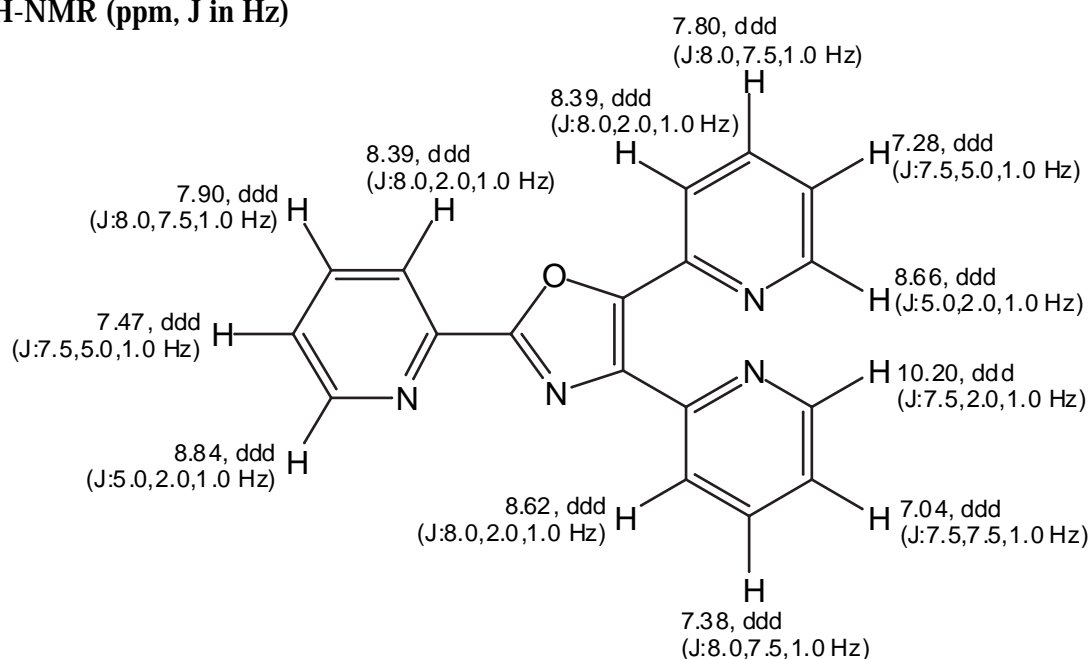
Table II

The Correlation between the reaction temperature and the yield of **2**
(under conditions used in Entry No.2, Table I)

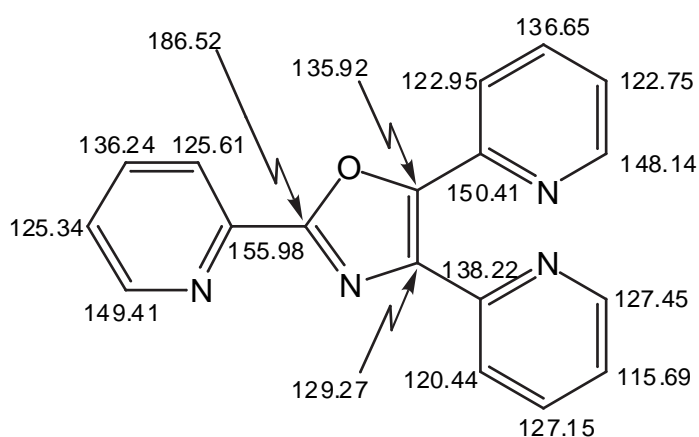
Entry	Reaction Temperature	Yield(%) of 2
1	Room Temperature	5
2	Heating at 90 °C	48

Chart 1

¹H-NMR (ppm, J in Hz)



¹³C-NMR (ppm)



The formation of **2** from **1** should depend on an intermolecular carbon-carbon bond formation by a radical coupling where the chelation between 2-aminomethylpyridine (**1**) and cobalt(II) ion, and participation of molecular oxygen are essential. In fact, when 3-aminomethylpyridine and 4-aminomethylpyridine in place of 2-aminomethylpyridine (**1**) were employed in this reaction under

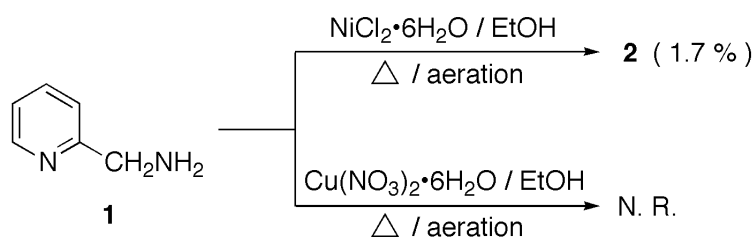
normal conditions, the starting amines were also recovered, respectively. Moreover, when the reaction carried out under a nitrogen stream, a blue color appeared, but the color never changed during the reaction, and 2-aminomethylpyridine (**1**) was finally recovered. Oxidation of **1** with potassium ferricyanide under a nitrogen stream gave a trace amount of **2** with many other by-products (checked by TLC), and the starting amine (**1**) was mostly recovered. The structures of **2** and **3** were established by MS and NMR spectral analyses (Chart 1 shows NMR data of **3**).

Table I shows the correlation between the molar ratio of 2-aminomethylpyridine (**1**) to cobalt(II) ion and the yield of the product (**2**). Although all cases provided **2**, the optimum yield was obtained when the ratio of **1** to cobalt(II) ion was three to one. Table II shows the correlation between reaction temperature and the yield of **2**. The reaction proceeded at room temperature, but it was more effective by heating on a water bath. On the contrary, the mild reaction temperature might be more preferable for the formation of **3**. Thus the optimum reaction conditions for synthesizing **2** were determined, however, we encountered an obstacle in the stage of extraction process. When reaction products were extracted with chloroform, emulsion occurred, and we had to use a centrifuge to separate it. However, when we employed ethanol as the reaction solvent in place of water, such a trouble was eliminated.

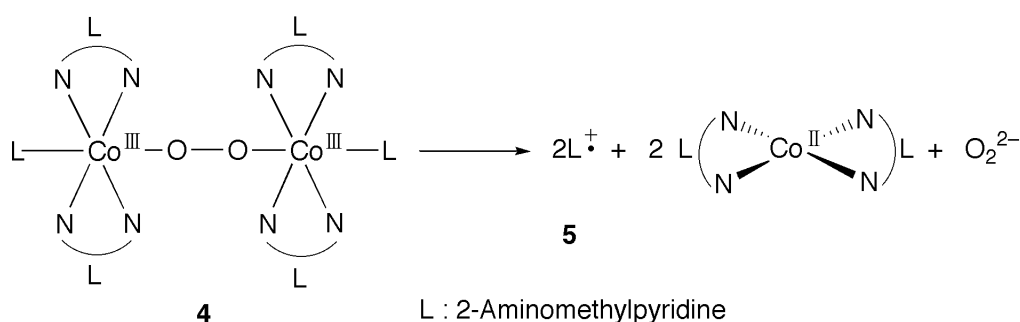
Other metal complexes using Group VIII (8-10) elements were also prepared as oxygen carrier.⁶ When nickel(II) ion was used in the above reaction, the yield of the product (**2**) was very much lower than that obtained using cobalt(II) ion. However, when copper(II) ion was used, no oxidation reaction occurred at all (Scheme 2).

Oxidation pathways of the reaction were considered and two possible pathways were proposed. One is that the complex of 2-aminomethylpyridine (**1**) with cobalt(II) ion readily reacts with molecular oxygen to provide μ -peroxodicobalt(III) complex (**4**), which undergoes irreversible reaction to provide a cation radical(**5**) as shown in Scheme 3. In fact, μ -peroxodicobalt(III)

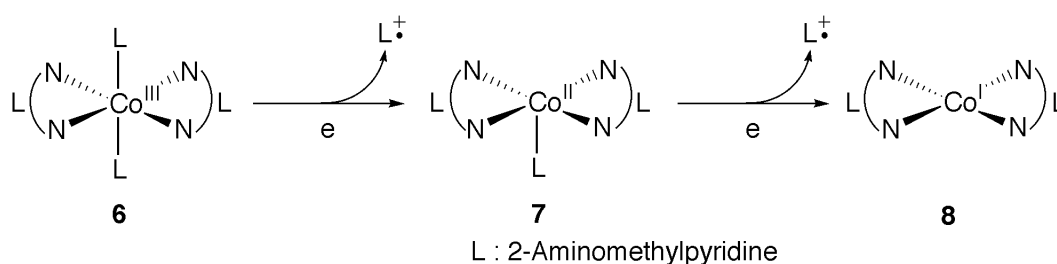
Scheme 2



Scheme 3



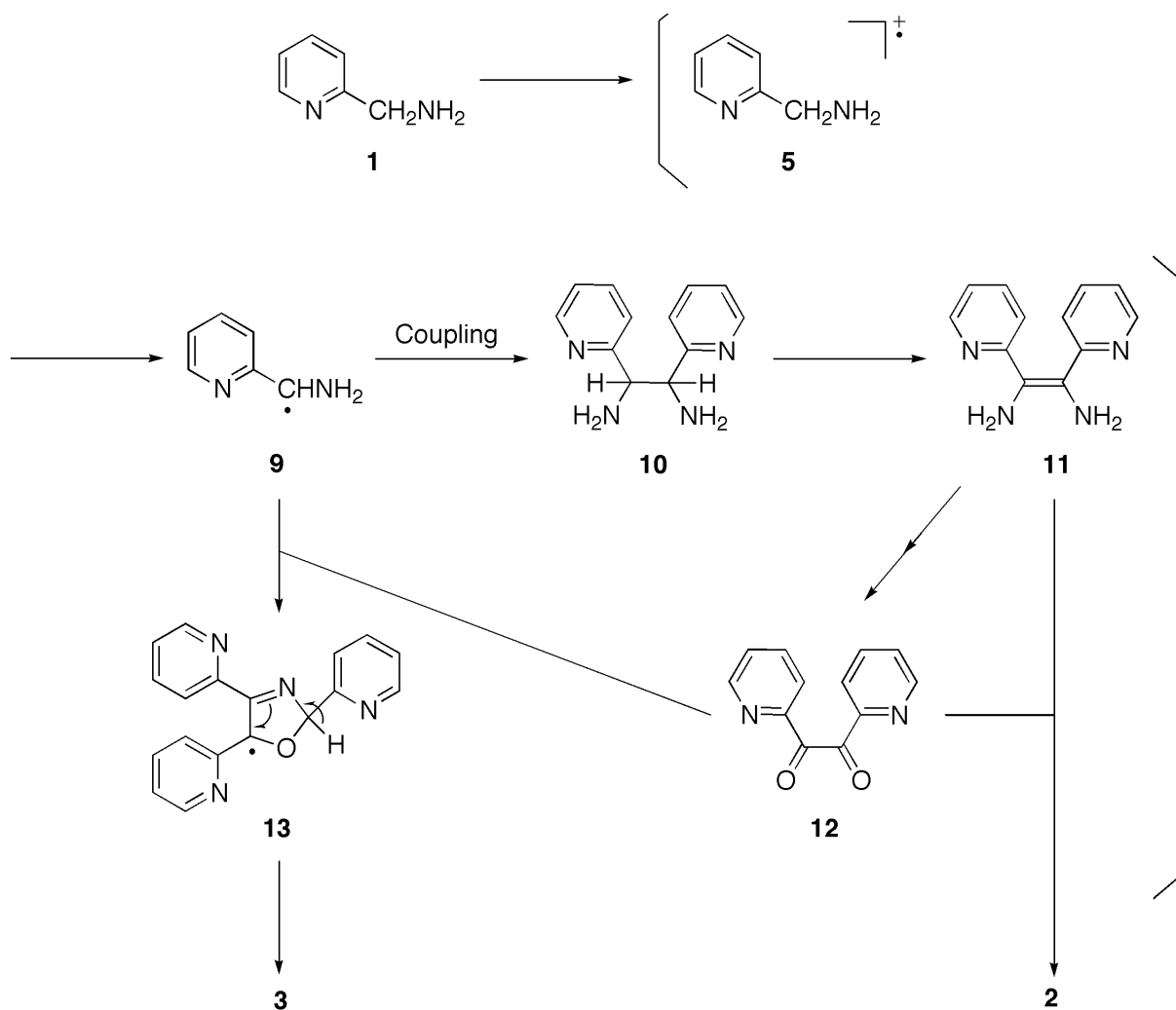
Scheme 4



complexes containing di-(2-pyridyl)ketone and 2',2'',2'''-tripyridyl ligands have been prepared by bubbling oxygen through a solution containing cobalt(II) ions, sodium perchlorate, and the ligands of the pyridine derivatives.⁷ On the other hand, Sargeson and his co-worker⁸ pointed out that the tightness and the steric bulk of the ligand structures prevent access of molecular oxygen to the hindered cobalt(II) center, and they synthesized macrotricyclic hexamine cage complexes of cobalt(III) by aerial oxidation of cobalt(II) ions in a solution of the ligand. Moreover, it is known that complexes of cobalt(III) with the sterically bulky ligands such as macromonocycle⁹ and vitamin B₁₂¹⁰ apparently exhibit reduction of the metal ion by two one-electron steps to produce cobalt(II) and then cobalt(I) complexes, and that such reductions are

accompanied by stereochemical change involving loss of axial ligands.¹¹ From this point of view, there is a possibility of the formation of cobalt(III) -1 complex (**6**) by the aerial oxidation of cobalt(II) ions in a solution of 2-aminomethylpyridine (**1**), and cation radical (**5**) may also be provided from **6** and **7** where L is 2-aminomethylpyridine (**1**) (Scheme 4). On the basis of these data, we propose reaction pathways in Scheme 5. The ligand (**1**) was oxidized to cation radical (**5**) which was converted to radical (**9**) by dehydrogenation. Intermolecular coupling of **9** gave **10** which was again oxidized to **11**. Oxidation followed by hydrolysis converted **11** to **12** which reacted with **11** to give **2**, while **12** reacted with **9** to give **13** which was dehydrogenated to provide **3**.

Scheme 5



EXPERIMENTAL

Melting points were determined using a Yamato Scientific stirred liquid apparatus and are uncorrected. The NMR spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The MS were obtained on JMS-O1S and DX-300 (equipped with JMA-3100) spectrometers (Japan Electron Optics Laboratory Co., Ltd.). Elemental analyses were performed on a Perkin-Elmer model 240B machine.

2,3,5,6-(Tetrapyridin-2-yl)pyrazine (**2**)

Procedure A (Synthesis in water); A solution of **1** (1 g, 9.2 mmol) in 50 mL of water was heated with stirring on a boiling water bath in the presence of cobalt(II) chloride hexahydrate (0.74 g, 3.1 mmol) for 3 h. The color of the solution changed during the reaction (first, blue and finally to reddish-brown), and the solution contained cobalt(II) complex of the product (**2**). The solution was extracted with chloroform (40 mL x 5). The extraction was also carried out from the solution which was made alkaline (above pH 11) by addition of 10% sodium hydroxide solution. When emulsion was formed during the process, a centrifuge was used for the separation. The extract was washed with a small amount of water, and dried over sodium sulfate. The solution was evaporated to dryness under reduced pressure. Chromatography was carried out on silica gel with chloroform-methanol (9:1) as eluent, and **2** (Rf 0.26) was obtained in 45% yield (0.40 g), mp 280-282 (with a trace amount of **3** (Rf 0.65), mp 140-141); MS: m/z 388 (M⁺); ¹H-NMR (CDCl₃): 8.38 (ddd, J=5.0, 2.0, 1.0 Hz, 4H, pyridine-6), 8.04 (ddd, J=8.0, 2.0, 1.0 Hz, 4H, pyridine-3), 7.79 (ddd, J=8.0, 8.0, 2.0 Hz, 4H, pyridine-4), 7.22 (ddd, J=8.0, 5.0, 1.0 Hz, 4H, pyridine-5); ¹³C-NMR (CDCl₃): 122.9 (pyridine-5), 124.4 (pyridine-3), 136.4 (pyridine-4), 148.5 (pyridine-6), 149.4 (pyrazine), 156.8 (pyridine-2). Anal. Calcd for C₂₄H₁₆N₆: C, 74.21; H, 4.15; N,

21.64. Found: C, 73.93; H, 4.03; N, 21.37.

Procedure B (An improved method); A solution of **1** (1 g, 9.2 mmol) in 10 mL of ethanol was added to a solution of cobalt(II) chloride hexahydrate (0.74 g, 3.1 mmol) in 50 mL of ethanol, and the mixture was refluxed on a boiling water-bath for 3.5 h under aeration. After removal of the solvent under reduced pressure, 50 mL of water was added to the residue, and the solution was basified with sodium carbonate (pH 11). The alkaline solution was extracted with chloroform (40 mL x 4), the extract was evaporated to dryness, and 17 mL of ethanol was added to the residue, then, the mixture was filtered off while it was hot to provide 0.40 g of pure golden plates of **2**. From the filtrate, crystals of **2** were obtained in 0.03 g (total yield 48%).

Procedure C (Synthesis in ethanol using nickel (II) chloride hexahydrate); A solution of **1** (1 g, 9.2 mmol) in 10 mL of ethanol was added to a solution of nickel(II) chloride hexahydrate (0.74 g, 3.1 mmol) in 50 mL of ethanol, and the mixture was refluxed on a boiling water bath for 3.5 h under aeration. After removal of the solvent under reduced pressure, 50 mL of water was added to residue, and the solution was basified with sodium carbonate (pH 11). The alkaline solution was extracted with chloroform (40 mL x 4), the extract was evaporated to dryness, and 0.5 ml of ethanol was added to the residue, then the mixture was filtered off to give 2.1 mg (0.23%) of pure crystals of **2**.

2,4,5-(tripyridin-2-yl)oxazole (3)

A mixed solution of **1** (1 g, 9.2 mmol) and cobalt (II) chloride hexahydrate (1g, 4.2 mmol) in 80 mL of water was warmed at 40 °C for 3 days under the air. The solution was extracted with chloroform (50 mL x 4 times) to provide **2** (R_f 0.26) and **3** (R_f 0.65) (checked by TLC; chloroform/methanol=9/1). The compound (**3**) was isolated by column chromatography using

silica gel in 1.7% yield (16 mg), mp 140-141 ; MS: m/z 300.100 (M⁺) [Calcd m/z 300.101 (M⁺)];
¹H and ¹³C-NMR (CDCl₃): See Chart 1. Anal. Calcd for C₁₈H₁₂N₄O: C, 71.99; H, 4.03; N, 18.66.
Found: C, 71.87; H, 4.23; N, 18.58.

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