HETEROCYCLES, Vol. 75, No. 2, 2008, pp. 297 - 304. © The Japan Institute of Heterocyclic Chemistry
Received, 9th August, 2007, Accepted, 17th October, 2007, Published online, 23rd October, 2007. COM-07-11197

ONE-POT SYNTHESIS OF INDOLIZINE DERIVATIVE AND ITS APPLICATION AS MULTI-DENTATE LIGAND

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Abstract – 1-Cyano-3-(2-pyridinecarboxamido)-2-(2-pyridiyl)indolizine (**2**) was readily synthesized by the one-pot reaction of 2-(cyanomethyl)pyridine (**1a**) with selenium dioxide. The reaction of 3- or 4-(cyanomethyl)pyridines (**1b,c**) under the same reaction conditions gave 2,3-bi(3-pyridyl)-2-butenedinitrile (**3b**) and 2,3-bi(4-pyridyl)-2-butenedinitrile (**3c**), respectively. The indolizine **2** (L-H) reacted with $Ni(NO_3)_2 \cdot 6H_2O$ in ethanol to produce the NiL_2 complex (**4**). The structure was determined by X-ray crystallography.

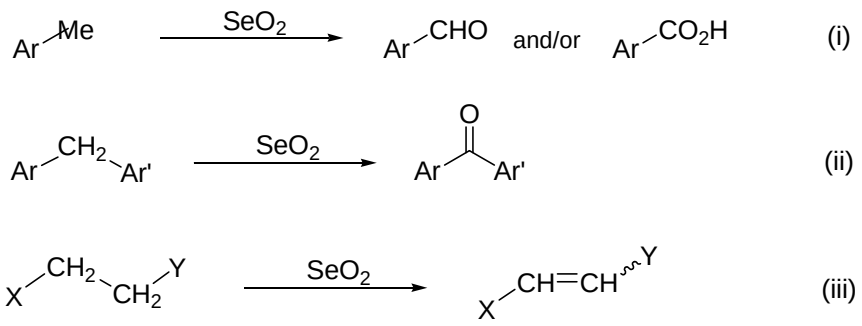
INTRODUCTION

Indolizine is a very important fused hetero aromatic ring for pharmaceutical and material science fields. For example, some 3-substituted indolizine-1-carbonitlile derivatives have activity against tyrosine phosphatases.[1] There are three typical methods for the syntheses of indolizine derivatives:[2] i) intra- and intermolecular condensation reactions, ii) 1,3-dipolar cycloadditions, and iii) 1,5-dipolar cyclizations. In addition, recently, many methods for the synthesis of the indolizine skeleton have been extensively studied.[1,3]

Previously, we reported the facile synthesis of tetrapyridylpyrazine from 2-(aminomethyl)pyridine in the presence of cobalt(II) chloride where methylene group adjacent to pyridine ring was easily oxidized by air.[4] In continuation of this work, we attempted to oxidize active methylene group of cyanomethylpyridines (**1**) by use of selenium dioxide.

Generally, methyl or methylene groups adjacent to aromatic or *N*-heterocyclic rings are converted to an aldehyde, carboxylic acid or ketone by selenium dioxide oxidation (eqs. i and ii).[5, 6] An ethylene group

adjacent to two activating groups is dehydrated to provide an olefin (eq. iii).[5]



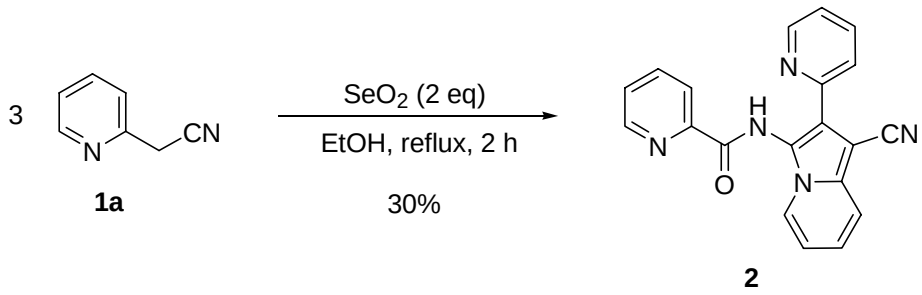
Ar, Ar': aryl group
X, Y: activating group (carbonyl, ester or aryl group)

This report describes a new one-pot synthesis of 1-cyano-3-amido-2-pyridiylindolizine (**2**) by the oxidation of 2-(cyanomethyl)pyridine (**1a**) with selenium dioxide. Herein, the coordination ability of **2** was also investigated.

RESULTS AND DISCUSSION

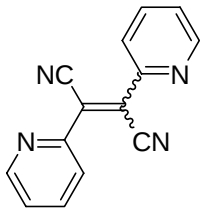
2-(Cyanomethyl)pyridine (**1a**) reacted with selenium dioxide (2 eq) in ethanol under reflux for 2 h to give the indolizine (**2**) (Scheme 1). This unique compound (**2**) can be purified by recrystallization or sublimation as colorless needles (yield 30%, mp 277 °C). The structure of **2** was determined by MS, IR, ^{1}H and ^{13}C NMR and elemental analysis. Furthermore, an X-ray structural analysis for the nickel complex (**4**) of **2** was carried out to verify the structure (vide infra).

Scheme 1



The IR spectra showed the stretching frequencies of the nitrile and amide carbonyl at 2211 and 1674 cm^{-1}, respectively. The ^{1}H NMR spectra showed the chemical shift of the amide N-H resonance at δ 12.03, which was easily exchanged with deuterium by the addition of deuterium oxide to the deuterated chloroform solution of **2**. The chemical shifts at δ 117.0 and 163.5 in the ^{13}C NMR spectra were assigned to the C≡N and amide C=O, respectively.

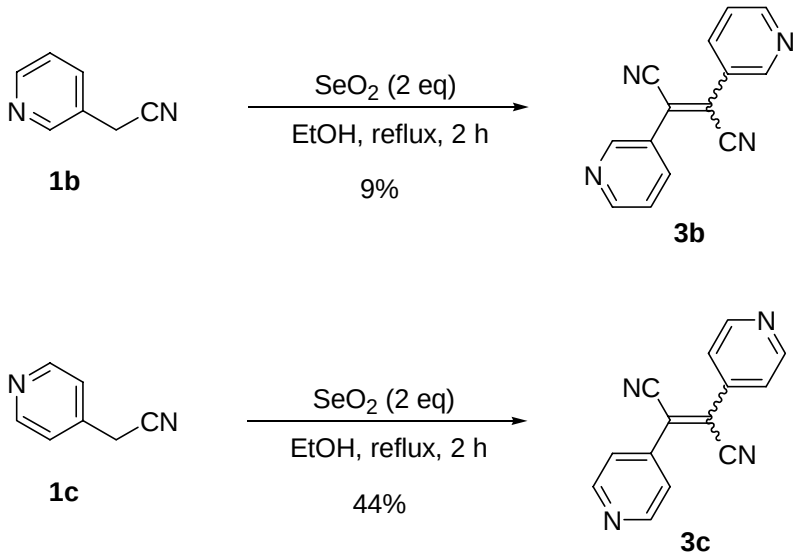
We attempted the reactions of 2-(cyanomethyl)pyridine with selenium dioxide under other reaction conditions. When the reactions were carried out at lower temperatures, the yields of **2** decreased. For example, at 25 °C, the crude product contained only a trace amount of **2** along with a trace of the dimeric product **3a**[7] showing a peak (m/z = 232) in the MS spectra. At 0 °C, the reaction did not proceed and the starting compound was recovered. Changing the amount of selenium dioxide also did not lead to higher yields of the desired product (yields of **2**: 21% at 1 eq, and 16% at 0.5 eq).



3a

On the other hand, the 3- and 4-(cyanomethyl)pyridines provided different results. Namely, the reactions using the 3- or 4-(cyanomethyl)pyridines (**1b** or **1c**) instead of 2-(cyanomethyl)pyridine produced no indolizines but only 2,3-bi(3-pyridyl)-2-butenedinitrile (**3b**) or 2,3-bi(4-pyridyl)-2-butenedinitrile[8] (**3c**), respectively (Scheme 2).

Scheme 2



1b **3b**

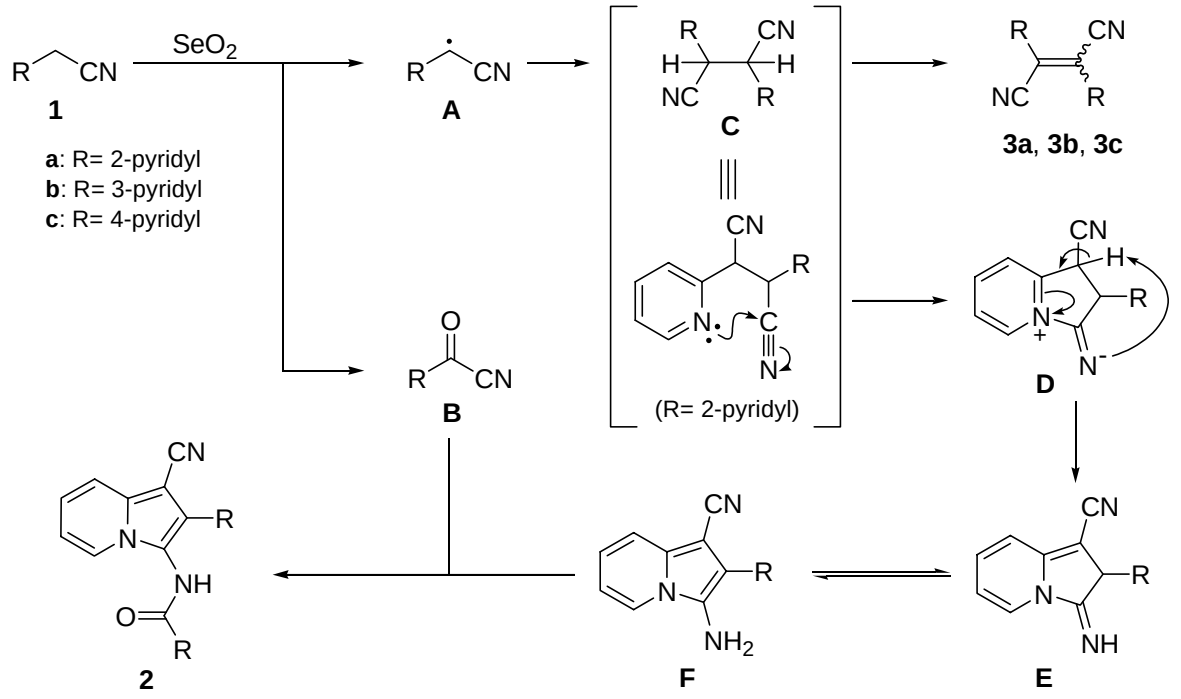
1c **3c**

These products were purified by silica gel column chromatography ($CHCl_3$) or recrystallization (EtOH) to give needles (yields: **3b** 9% and **3c** 44%, respectively).

In these reactions, the position of the cyanomethyl group on the pyridine ring significantly influenced the reaction products. The possible mechanisms for the reactions of the 2-, 3- and 4-cyanomethylpyridines with selenium dioxide are shown in Scheme 3. At first, the substrates are oxidized by selenium dioxide

to afford the cyanopyridylmethyl radical **A** and then the dimeric intermediate **C** by radical coupling. For the 2-cyanomethylpyridine, the nitrogen atom on the pyridine attacks the carbon of the cyano group to form the five-membered ring **D** which isomerizes to **F** via **E** through a proton shift. The intermediate **F** reacts with a cyano ketone **B**, which is afforded by the oxidation of the starting cyanomethylpyridine, to give the final product **2**. Under the same conditions, the 3- and 4-(cyanomethyl)pyridines provided 2,3-bipyridyl-2-butenedinitriles **3b** and **3c**, respectively, by the dehydrogenation of **C**.

Scheme 3



Compound **2** (L-H) is very interesting for complex chemistry, as **2** have many coordinating sites, such as the pyridyl, cyano and amido groups. The structure of **2** might be very flexible in order to take various coordination forms. The transition metal complexations with **2** as a multi-dentate ligand were tried under several conditions. As a result, **2** was treated with $Ni(NO_3)_2 \cdot 6H_2O$ (0.5 eq) in ethanol at ambient temperature for 1 h to form the Ni(II) complex, NiL_2 (**4**), as orange crystals (yield 71%). The X-ray crystal structural analysis revealed that the complex adopted a distorted octahedral geometry, in which six nitrogen atoms coordinated (Figure 1). In the complex, the two indolizinyl amidato ligands coordinate to the nickel(II) atom as a tridentate meridional ligand via one amidato-nitrogen and two pyridine-nitrogen atoms. The bite angles, N1-Ni1-N2 and N4-Ni1-N5, of this complex are 89.59(14)° and 90.00(14)°, respectively. On the other hand, the bite angles, N2-Ni1-N3 and N5-Ni1-N6, are 78.25(14)° and 78.42(15)°, respectively, suggesting a significantly distorted geometry around the nickel. The amide group and the connected pyridine ring are almost coplanar (N2-C15-C16-N3: 6.3(6)°, N5-C35-C36-N6: 5.0(5)°), while the indolizine plane and the amide plane are non-coplanar, having

torsion angles of -46.7(6)° (N7-C7-N2-C15) and -46.6(6)° (N9-C27-N5-C35). The pyridine ring on the indolizine is slightly out of plane of the indolizine (N1-C5-C6-C7: 23.0(7)° and N4-C25-C26-C27: 28.1(6)°). One of the five-membered rings of the indolizine groups (N7-C7-C6-C13-C12) is close to a hydrogen atom (H22) on C38 of another molecule (N7···H22': 2.723 Å, Figure 2). This indicates that the C-H/π interaction is intermolecularly established. The value of the N7···H22' distance is similar to the sum of the Van der Waals radii of the nitrogen and hydrogen atoms (2.75 Å),[9] and is within the range of the typical ones of the C-H/π interaction.[10]

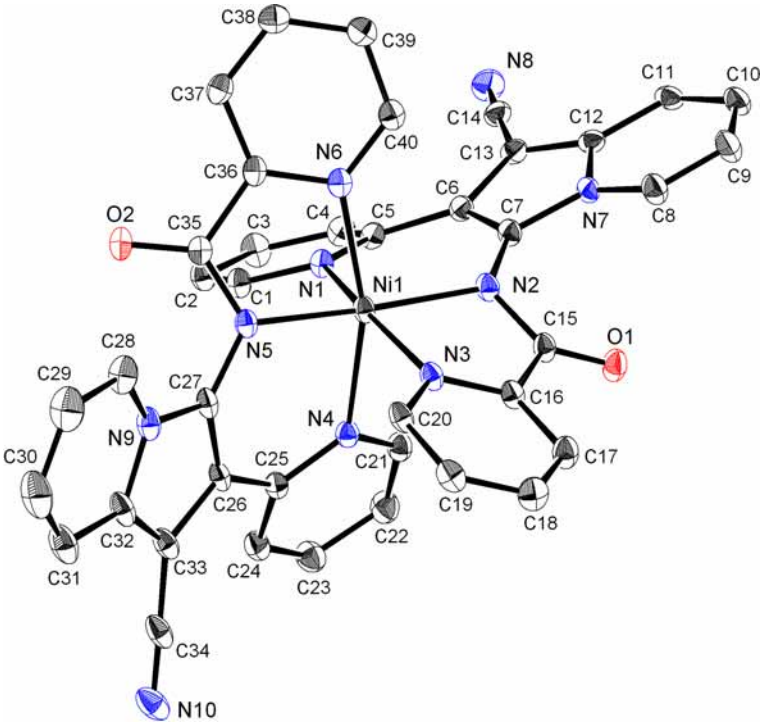


Figure 1. ORTEP drawing of nickel complex NiL_2 (**4**). All hydrogen atoms and crystalline solvent molecules (chloroform) are omitted for clarity.

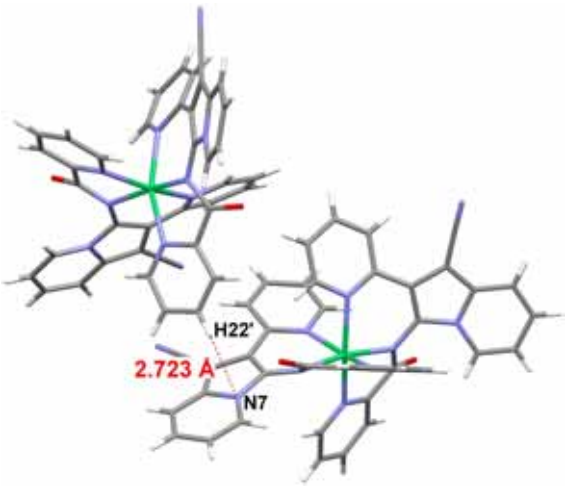


Figure 2. Intermolecular C-H/π interaction in the complex NiL_2 (**4**).

In this study, we found that the one-pot reaction of 2-(cyanomethyl)pyridine (**1a**) with selenium dioxide readily afforded the 1-cyano-3-(2-pyridinecarboxamido)-2-(2-pyridiyl)indolizine (**2**). This indolizine **2** (L-H) reacted with $Ni(NO_3)_2 \cdot 6H_2O$ to give the complex NiL_2 (**4**). In complex **4**, each ligand is chelated to Ni(II) in an N3 tridentate fashion.

EXPERIMENTAL

The melting points were determined using a Yazawa Scientific micromelting point apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded by a Varian XL-400 spectrometer at 400 and 100 MHz, respectively. The IR spectra were measured by a JASCO FT/IR-410. The MS spectra were obtained using JMS-O1S and DX-300 (equipped with JMA-3100) spectrometers (Japan Electron Optics Laboratory Co., Ltd.). The X-ray crystallographic analysis of **4** was carried out using a Rigaku Mercury CCD diffractometer. The structures for **4** were solved by direct methods using SHELXL-97.

1-Cyano-3-(2-pyridinecarboxamido)-2-(2-pyridiyl)indolizine (2): Selenium oxide (1.88 g, 16.9 mmol) was dissolved in hot EtOH (140 mL) and then cooled to rt. An EtOH (10 mL) solution of 2-(cyanomethyl)pyrideine **1a** (1.00 g, 8.46 mmol) was added dropwise to the solution of selenium dioxide. The colorless solution was heated under reflux conditions for 2 h. After cooling to ambient temperature and then -10 °C, the reaction mixture was decanted and dried under vacuum to give a dark brown solid. The solid was dissolved in $CHCl_3$ (30 mL) and stirred for 30 min. The insoluble parts were filtered off and the filtrate was concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$) and recrystallization (EtOH) to give the pure product **2** as colorless needles (0.287 g, 30%). Mp 277 °C. IR (KBr): 3441, 2211 ($\nu_{C\equiv N}$), 1674 ($\nu_{C=O}$), 1594, 1495, 1361, 1260, 997, 784, 741, 618, 493 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 6.85 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H), 7.14 (ddd, J = 9.0, 7.0, 1.0 Hz, 1H), 7.21 (ddd, J = 8.0, 5.0, 1.0 Hz, 1H), 7.54 (ddd, J = 8.0, 5.0, 1.0 Hz, 1H), 7.71 (ddd, J = 9.0, 1.0, 1.0 Hz, 1H), 7.80 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H), 7.91 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H), 7.96 (ddd, J = 7.0, 1.0, 1.0 Hz, 1H), 8.09 (ddd, J = 8.0, 1.0, 1.0 Hz, 1H), 8.24 (ddd, J = 8.0, 1.0, 1.0 Hz, 1H), 8.71 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H), 8.77 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H), 12.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 78.9, 113.0, 117.0, 117.6, 119.3, 120.0, 122.2, 122.7, 122.8 (two peaks overlapped), 125.5, 126.9, 136.3, 137.2, 137.5, 148.7, 149.0, 149.1, 151.5, 163.5. Anal. Calcd for $C_{20}H_{13}N_5O$: C, 70.79; H, 3.86; N, 20.64. Found: C, 70.75; H, 3.96; N, 20.50. MS (EI): m/z = 339 (M^+), 261, 233, 78.

2,3-Bi(3-pyridyl)-2-butenedinitrile (3b): To a solution of selenium dioxide (4.10 g, 37.0 mmol) in EtOH (80 mL), 3-(cyanomethyl)pyridine **1b** (2.19 g, 18.5 mmol) was added. The reaction mixture was heated under reflux for 2 h, and then filtered to remove the reddish brown precipitates. The filtrate was concentrated in vacuo, giving a brown oily substance. The crude product was dissolved in $CHCl_3$, and the insoluble parts were filtered off. The chloroform solution was washed with 5% aq. $NaHCO_3$ (100

mL) and water (50 mL), dried with Na_2SO_4 and evaporated under reduced pressure. Purification by silica gel column chromatography ($CHCl_3$) gave the pure **3b** as yellow crystals (0.196 g, 9.1%). Mp 140 °C. IR (KBr): 3047, 2219 ($\nu_{C\equiv N}$), 1585, 1563, 1475, 1412, 1335, 1258, 1186, 1128, 1014, 955, 924, 849, 802 705, 659, 617, 584 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 7.68 (ddd, J = 8.0, 5.0, 1.0 Hz, 1H, H^5 of py), 8.26 (ddd, J = 8.0, 2.5, 1.5 Hz, 1H, H^4 of py), 8.80 (dd, J = 5.0, 1.5 Hz, 1H, H^6 of py), 9.04 (dd, J = 2.5, 1.0 Hz, 1H, H^2 of py). ^{13}C NMR (100 MHz, DMSO-d_6): 116.0, 124.11, 124.3, 128.3, 136.5, 149.0, 152.3. Anal. Calcd for $C_{14}H_8N_4$: C, 72.40; H, 3.47; N, 24.12. Found: C, 72.25; H, 3.66; N, 23.79. MS (EI): m/z = 232 (M^+), 204, 179. HRMS (FAB+) Calcd for $C_{14}H_9N_4$ ($M+H^+$): 233.0827; Found: 233.0827.

2,3-Bi(4-pyridyl)-2-butenedinitrile (3c)[8]: To a suspension of 4-(cyanomethyl)pyridine hydrochloride **1c**·HCl (1.40 g, 9.06 mmol) in EtOH (10 mL), a solution of KOH (0.51 g, 9.09 mmol) in EtOH (35 mL) was added and the mixture was stirred at rt. After 24 h, a filtration giving a red solution was followed by the addition of selenium dioxide (2.01 g, 18.1 mmol) in EtOH (10 mL). The reaction mixture was heated under reflux for 2 h, and then filtered to remove the precipitates. The filtrate was gradually cooled, giving colorless needles of the pure **3c** (0.46 g, 44%). Mp 232-233 °C (lit.,[8b] 232 °C). IR (KBr): 3045, 2228 ($\nu_{C\equiv N}$), 1586, 1544, 1410, 1255, 1218, 1068, 987, 865, 814, 633, 580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 8.89 (dd, J = 4.0, 2.0 Hz, 2H, H^2 of py), 7.74 (dd, J = 4.0, 2.0 Hz, 2H, H^3 of py). ^{13}C NMR (100 MHz, $CDCl_3$): 115.1, 122.2, 126.1, 137.5, 151.5. HRMS (FAB+) Calcd for $C_{14}H_9N_4$ ($M+H^+$): 233.0827; Found: 233.0829.

Ni Complex (4): A solution of $Ni(NO_3)_2·6H_2O$ (13 mg, 0.045 mmol) in EtOH (10 mL) was added to a solution of **2** (31 mg, 0.090 mmol) in $CHCl_3$ (10 mL) and stirred at rt. After stirring for 1 h, the reaction mixture was concentrated under reduced pressure to give a crude product. Purification by silica gel chromatography ($CHCl_3$/MeOH = 9:1) yielded **4** as an orange solid (71%). Recrystallization from $CHCl_3$/EtOH gave orange needles suitable for the X-ray single crystal structural analysis.[11]

ACKNOWLEDGEMENTS

This research was partly financially supported by the Sasakawa Scientific Research Grant from The Japan Science Society.

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11. The complex **4** was recrystallized containing two molecules of chloroform as crystalline solvents per one molecule of **4**. Main crystallographic data for **4** · 2 $CHCl_3$: $C_{42}H_{26}Cl_6N_{10}NiO_2$, M = 974.14, space group I41/a, Tetragonal, a = 38.510(10), b = 38.510(10), c = 11.513(3) Å, V = 17074(7) $Å^3$, T = 113(2) K, Z = 16, D_{calc} = 1.516 g/cm^3, 9029 reflections with $I \geq 2\sigma(I)$, 551 refined parameters. The final R is 0.1029. CCDC 656423 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.