Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *81* (12) 1383–1392 (2016)
JSCS–4935
UDC 546.982+547.587.51+547.466.22:548.7:66.094.941
Original scientific paper

Synthesis and characterization of palladium(II) complexes with glycine coumarin derivatives

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(Received 15 September, revised 25 September, accepted 27 September 2016)

Abstract: A Pd(II) complex with methyl 2-([1-{2,4-dioxochroman-3-ylidene}-ethyl]amino)acetate was synthesized. The structures of both the ligand and its Pd(II) complex were determined by elemental analysis, and IR and NMR spectroscopy. Recrystallization of the Pd(II) complex from DMF/water solution resulted in its hydrolysis and the formation of the dimethylamine (2-[{1-(2,4--dioxochroman-3-ylidene)ethyl}amino]acetato)palladium(II) complex, the structure of which was determined by elemental analysis, IR, ^{1}H- and ^{13}C-NMR spectroscopy and X-ray analysis.

Keywords: coumarin-derived ligands; crystal structure; mechanism of hydrolysis.

INTRODUCTION

Coumarins (derivatives of 2*H*-1-benzopyran-2-one) are of great interest in medicinal chemistry because of their wide range of pharmacological activity.[1–6] Metal complexes with coumarin derivatives have been investigated because of their anticoagulant,[7] antimicrobial[8] and antitumor activities.[9–11] Among the complexes with coumarin derivatives, Pd(II) complexes have attracted considerable attention because of their significant antitumor activity.[12–15] Following these findings, in this work the synthesis of methyl 2-([1-{2,4-dioxochroman-3-ylidene}ethyl]amino)acetate (**HL1**) and its chlorido Pd(II) complex (**1**) are reported. Attempts to obtain monocrystals of complex **1** from DMF/water solution resulted in its hydrolysis and the formation of dimethylamine(2-[{1-(2,4-dioxochroman-

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doi: 10.2298/JSC160915087S

-3-ylidene)ethyl}amino]acetato) palladium(II) complex (**2**). All the obtained compounds were characterized by elemental analysis, and IR and NMR spectroscopy. The crystal structure of complex **2** was determined by X-ray analysis.

EXPERIMENTAL

Materials and methods

Hydrochlorides of glycine and glycine methyl ester, triethylamine, methanol, ethanol, toluene, acetone and potassium tetrachloridopalladate(II) were obtained from Sigma–Aldrich. 3--Acetyl-4-hydroxycoumarin was synthesized according to a previously described procedure.[16]

Elemental analyses were performed on a Vario EL III C,H,N elemental analyzer. Melting points of the ligands were determined using a Kofler hot stage apparatus. IR spectra were run on a Perkin–Elmer Spectrum One FT-IR spectrometer using the KBr pellet technique (4000––400 cm^{-1}). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra of the **HL^1** ligand were recorded on a Varian Gemini 200 spectrometer (Varian, Palo Alto, CA, USA) in $CDCl_3$ using TMS as an internal standard for ^{1}H and ^{13}C. The ^{1}H-NMR (500 MHz) spectrum of complex **1** was recorded on a Bruker Avance 500 spectrometer in DMSO-d_6 using TMS as an internal standard. Due to the low solubility of complex **1** in DMSO, it was not possible to obtain its ^{13}C-NMR spectrum. ^{1}H-NMR (500 MHz), ^{13}C NMR (125 MHz) and 2D NMR spectra (COSY, HSQC) of complex **2** were recorded on a Bruker Avance 500 spectrometer in DMSO-d_6 using TMS as an internal standard for ^{1}H and ^{13}C. Analytical TLC was performed on silica gel (Silica gel 60, layer 0.20 mm, Alugram Sil G, Macherey–Nagel, Germany). The visualization of TLC plates was performed using a UV lamp at 254 and 365 nm (VL-4.LC, 365/254, Vilber Lourmat, France). Characterization data are of synthesized compounds are given in Supplementary material to this paper.

*Synthesis of methyl 2-([1-{2,4-dioxochroman-3-ylidene}ethyl]amino)acetate (**HL^1**)*

A mixture of 3-acetyl-4-hydroxycoumarin (0.5 g, 2.45 mmol), the hydrochloride of glycine methyl ester (2.45 mmol) and trimethylamine (0.2 g, 2.00 mmol) in methanol (50 mL) was refluxed for 2 h. The progress of the reaction was monitored by TLC (toluene:acetone volume ratio of 8:2). After completion of the reaction, evaporation of solvent to half of the volume and addition of 5 mL of water, the obtained white solid was filtered, dried and recrystallized from 96 % ethanol.

*Synthesis of 2-([1-{2,4-dioxochroman-3-ylidene}ethyl]amino)acetic acid (**H_2L^2**)*

Into a solution of 3-acetyl-4-hydroxycoumarin (0.5 g, 2.45 mmol) in methanol (50 mL), glycine (0.18 g, 2.45 mmol) was added. The pH of the reaction mixture was adjusted by the addition of three drops of conc. HCl. The clear, colorless solution was refluxed for 3 h. After six days, a white solid precipitated from the reaction solution.

*Synthesis of chlorido(methyl 2-[{1-(2,4-dioxochroman-3-ylidene)ethyl}amino]acetate) palladium(II) complex (**1**)*

Potassium tetrachloridopalladate(II) (0.05 g, 0.153 mmol) was dissolved in 10 mL of water and the same amount of enamine **HL^1** (0.153 mmol) dissolved in methanol (10 mL) was added. The mixture was stirred for 3 h whereby a yellow precipitate was obtained. The precipitate of complex **1** was filtered off and washed with a small amount of methanol.

*Synthesis of dimethylamine(2-[{1-(2,4-dioxochroman-3-ylidene)ethyl}amino]acetato)-palladium(II) complex (**2**)*

Recrystallization of complex **1** from DMF/water (1:1 volume ratio) during seven days at room temperature resulted in the formation of crystals of complex **2**.

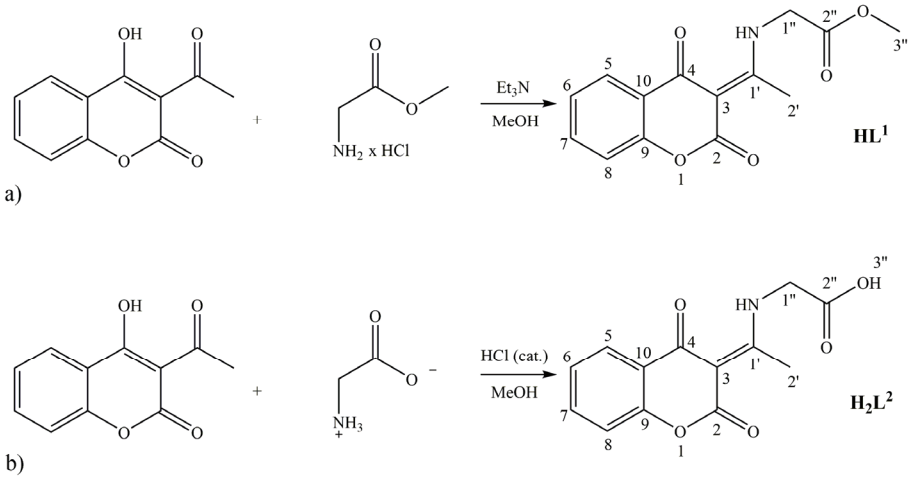
Crystallographic structure determination

Single crystal X-ray diffraction data were collected using MoKα radiation (λ = 0.71073 Å) at T = 293 K on an APEX2 diffractometer with CCD area detector. The collected intensities were corrected for Lorentz and polarization factors and empirically for absorption using the SADABS program.[17] Structures were solved by direct methods using SIR2011[18] and refined by full-matrix least-squares on all F^2 using SHELXL97[19] implemented in the Olex2 package.[20] Hydrogen atoms were introduced in the calculated positions. Anisotropic displacement parameters were refined for all non-hydrogen atoms. Hydrogen bonds were analyzed with SHELXL97[19] and use was made of the Cambridge Crystallographic Data Centre packages[21] for analysis of crystal packing. The crystal data and structure determination results are summarized in Table S-I of the Supplementary material to this paper.

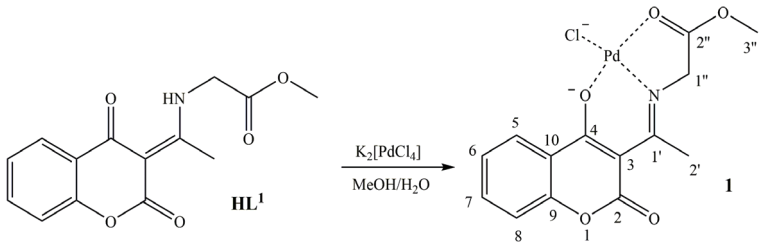
RESULTS AND DISCUSSION

Synthesis

Reaction of equimolar amounts of 3-acetyl-4-hydroxycoumarin and hydrochloride of glycine methyl ester in the presence of triethylamine in refluxing methanol yielded ligand **HL^1** (Scheme 1a). Ligand **H$_2$L^2** was obtained in the reaction of 3-acetyl-4-hydroxycoumarin and glycine in methanol in the presence of a catalytic amount of hydrochloric acid (Scheme 1b). Complex **1** was synthesized in the reaction of ligand **HL^1** and potassium tetrachloridopalladate(II) in a 1:1 mole ratio in water/methanol (1:1 volume ratio) solution (Scheme 2). Complex **2** was obtained during the recrystallization of complex **1** from DMF/water mixture. In addition, an attempt was made to synthesize complex **2** in the reaction of ligand **H$_2$L^2**, potassium tetrachloridopalladate(II) and dimethylamine or its hydrochloride in a 1:1:1 mole ratio in water/methanol (1:1 volume ratio) solution. Unfortunately, complex **2** could not be obtained in this way under any experimental conditions.



Scheme 1. Synthesis of ligands **HL^1** and **H$_2$L^2**.



Scheme 2. Synthesis of Pd(II) complex **1**.

IR spectra

The IR spectrum of **HL1** showed a broad band at 3406 cm^{-1} corresponding to the stretching vibrations of the NH group. Stretching vibrations of the carbonyl group of glycine methyl ester and coumarin lactone were observed at 1748 and 1720 cm^{-1}, respectively.

In the IR spectrum of $\mathbf{H_2L^2}$, the broad band at 3502 cm^{-1} corresponds to vibrations of the OH group from its carboxylic part and vibration of the NH group. This band was absent in the IR spectrum of complex **2**, indicating coordination of ligand in deprotonated form. Instead of this, a sharp band appeared at 3227 cm^{-1}, corresponding to stretching vibrations of NH from coordinated dimethylamine. Coordination of carboxylate resulted in a bathochromic shift of ν(C=O) from 1740 cm^{-1} in the spectrum of the $\mathbf{H_2L^2}$ ligand to 1690 cm^{-1} in the spectrum of complex **2**. A band at 1650 cm^{-1} originating from the imino group ν(C=N) of the uncoordinated ligand was shifted to 1660 cm^{-1}. Moreover, coordination of the deprotonated enol group of $\mathbf{H_2L^2}$ resulted in a shift of ν(C–O) from 1224 cm^{-1} in the spectrum of $\mathbf{H_2L^2}$ to 1245 cm^{-1} in the spectrum of complex **2**.

NMR spectra

In the ^{1}H-NMR spectrum of ligand **HL1**, the signal of the methyl protons from C2′ appeared at 2.70 ppm, while the signal of the methyl protons from the ester group (H3″) was observed at 3.86 ppm. The ^{1}H-NMR spectrum of **HL1** showed resonances at 12.51 and 14.65 ppm corresponding to the OH and NH groups of its tautomers, respectively. The observed δ value of the NH proton indicates *E* conformation of **HL1** and intramolecular hydrogen bonding with the keto oxygen atom.[22] Previously reported X-ray and DFT study of chromone derivatives showed that the keto tautomer with N–H···O hydrogen bonds is energetically more stable than the enol form containing O–H···N hydrogen bonds.[23] Based on these results, it could be assumed that the keto form is the main tautomeric form of the **HL1** ligand.

In the ^{13}C-NMR spectrum of ligand **HL1**, the C1′ carbon showed resonance at 177.5 ppm, whereas the signal of the methyl carbon C2′ was noted at 18.9 ppm. The signals of two carbonyl groups from the 2,4-dioxochroman moiety, lactone (C2) and ketone (C4), appeared at 162.5 ppm and 182.2 ppm, respectively.

In the ^{1}H-NMR spectrum of complex **1**, signals of hydrogen atoms from the OH and NH groups (12.51 and 14.65 ppm, respectively) of the ligand were absent, indicating that the ligand was coordinated in the deprotonated form. Coordination of **HL^1** through the nitrogen atom from the imino group resulted in downfield shift of the signals of methyl H2′ and methylene H1″ hydrogen atoms. In the ^{1}H-NMR spectrum of complex **1**, the signal of the methyl group from the ester part of the ligand was shifted upfield, indicating that the ester carbonyl oxygen was involved in the coordination. Coordination of the oxygen atom from C4 of the coumarin moiety resulted in an upfield shift of the H5 signal and downfield shifts of the H6, H7 and H8 signals.

From the ^{1}H-NMR spectrum of complex **2**, it could be seen that the ligand **H_2L^2** was coordinated in the deprotonated form since the signals of acidic protons were absent. The signal of the hydrogen atoms from the methylene group H1″ was shifted downfield due to coordination of the carboxylate oxygen atom. Coordination of ligand through the nitrogen atom of the imino group resulted in an upfield shift of the methyl H2′ signal. The upfield shift of the H5 signal and the downfield shift of the H6, H7 and H8 signals indicate coordination of the oxygen atom at C4 in the coumarin moiety. The signals of methyl groups and NH from dimethylamine ligand appeared at 2.40 and 2.52 ppm, respectively. Thus, the NMR spectral data indicated coordination of ligand **H_2L^2** *via* the imine nitrogen atom, the oxygen atom from C4 and the carboxylic oxygen atom.

*X-Ray crystallographic analysis of complex **2***

In complex **2** (Fig. 1), the Pd(II) cation is coordinated by one ligand molecule through the oxygen atom of the keto group from the 2,4-dioxochromane moiety, through the iminic nitrogen atom, and through the carboxylic oxygen atom; one molecule of dimethylamine completes the metal environment, where the square planar coordination of the metal cation shows two oxygen atoms and two nitrogen atoms respectively opposed. A non-coordinating water molecule

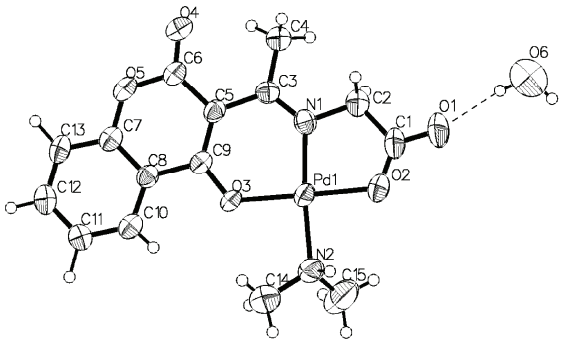


Fig. 1. Molecular structure and atom labeling of compound **2**. Thermal ellipsoids are at the 50 % probability level.

completes the asymmetric unit. A Mogul[21] check of the molecular geometry showed no significant deviations from the CCDC average values for all the bonding parameters, apart from the angles C4–C3–N1, O5–C6–O4 and C15–N2–C14, which are statistically smaller than the average, probably due to the mutual repulsion of C4 and O4, and to the coordination of N2.

The association of molecules in the crystal is driven by intermolecular hydrogen bonds between the coordinated dimethylamine N2–H and the carboxylate O1 (N2···O1(*i*) = 2.997(8) Å, N2–H···O1(*i*) = 157(5)°, *i* = –*x*+2, –*y*+1, –*z*), forming a supramolecular centro-symmetric dimer; the dimers are bridged by water molecules acting as hydrogen bond donors, interacting with the carboxylate oxygen O1 (O6··O1 = 2.84(1) Å, O6–H···O1 = 142.1(9)°) and the carbonylic O4 of an adjacent molecule (O6··O4(*ii*) = 3.00(1)Å, O6–H···O4(*ii*) = = 172.1(9)°, *ii* = *x*+1/2, –*y*+1/2, *z*–1/2), forming layers which expose the dimethylamine methyl groups and the water oxygens at the surfaces (Fig. 2).

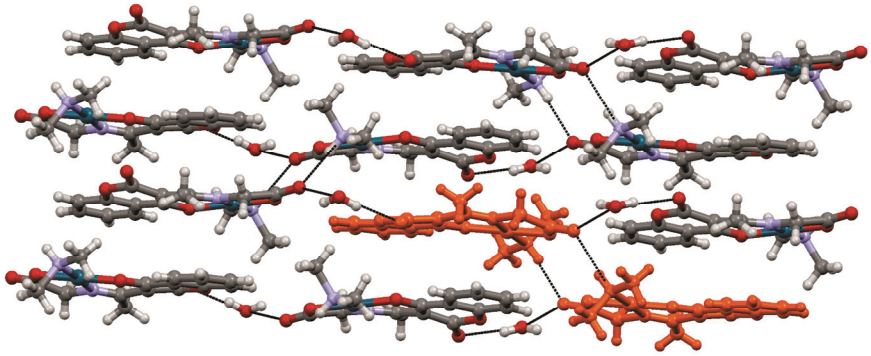
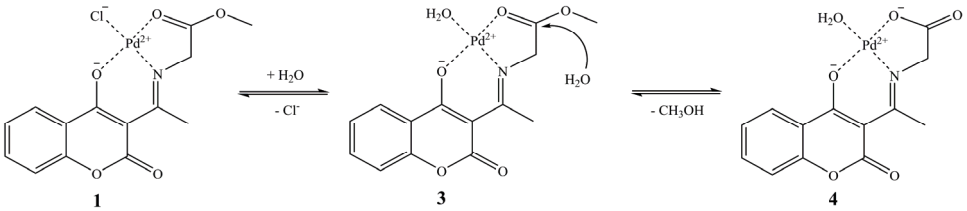


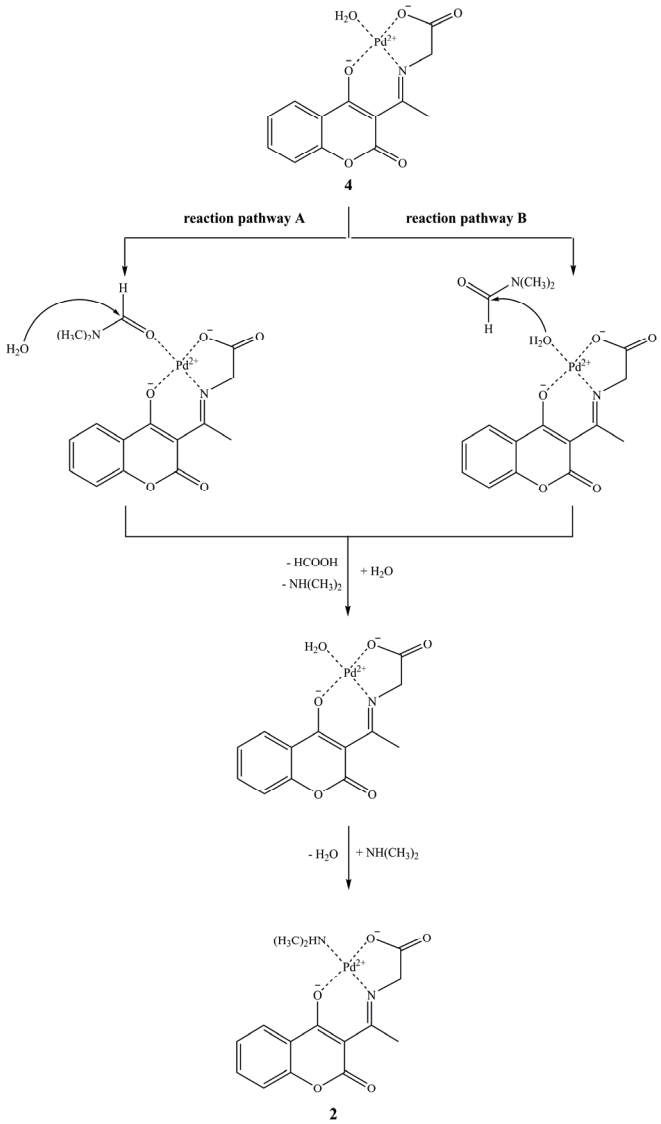
Fig. 2. Crystal packing of compound **2**, showing hydrogen bond layers made of dimers (in orange) bridged by water molecules.

Reaction mechanism

Considering the mechanism of the hydrolysis reaction that occurred during the recrystallization of complex **1** in the DMF/water solution, it could be assumed that the cationic complex **3** was initially formed in the substitution reaction between the chlorido ligand and a water molecule (Scheme 3). In complex **3,** Pd(II) acts as a Lewis acid, which polarizes the ester carbonyl group and activates its carbon atom toward attack by a water molecule from the solvent. Hydrolysis of the ester group of complex **3** leads to the formation of the neutral complex **4**, which catalyzes the hydrolysis of the amide bond of dimethylformamide. There are two possible reaction pathways (A and B) for the hydrolysis of dimethylformamide by complex **4** (Scheme 4). One of them (pathway A) involves the substitution of water molecule with carbonyl group of dimethylformamide, which is followed by an external attack of the polarized amide carbon atom by a



Scheme 3. Mechanism of ester bond hydrolysis in complex **1**.



Scheme 4. Mechanism of amide bond hydrolysis catalyzed by complex **4**.

water molecule from the solvent. In the second possible reaction pathway (pathway B), coordination of water molecule to Pd(II) in complex **4** enhances its nucleophilicity and facilitates its attack of the amide carbon atom of uncoordinated dimethylformamide. The replacement of the water molecule in complex **4** by the dimethylamine formed in the hydrolysis reaction led to the formation of complex **2**.

CONCLUSIONS

The synthesis and structural characterization of methyl 2-([1-{2,4-dioxochroman-3-ylidene}ethyl]amino)acetate (**HL^1**) and 2-([1-{2,4-dioxochroman-3--ylidene}ethyl]amino)acetic acid (**H$_2$L^2**) are presented herein for the first time. Complex **1** was synthesized in the reaction of the **HL^1** ligand and potassium tetrachloridopalladate(II) (mole ratio 1:1). Recrystallization of complex **1** from a DMF/water solution produced complex **2**. X-Ray crystallographic analysis of complex **2** showed that the Pd(II) cation was coordinated by one **HL^1** ligand molecule through the oxygen atom of the keto group from the 2,4-dioxochromane moiety, through the iminic nitrogen atom, and through the carboxylic oxygen atom. The square planar environment around the metal ion was completed with one molecule of dimethylamine. During the *in situ* synthesis starting from potassium tetrachloridopalladate(II), ligand **H$_2$L^2** and dimethylamine or its hydrochloride complex **2** were not obtained. Considering the mechanism of the hydrolysis reaction that occurred during the recrystallization of complex **1** from the DMF/water solution, two possible reaction pathways (A and B) for the hydrolysis of dimethylformamide catalyzed by Pd(II) were proposed.

SUPPLEMENTARY MATERIAL

Crystallographic data (excluding structure factors) for compound **2** were deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 1503280. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Crystal data, structure refinement for **2** and the IR and NMR data for the synthesized compounds are available electronically at the pages of journal website: http:////www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgements. This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant OI 172055 and Grant OI 172016).

ИЗВОД

СИНТЕЗА И КАРАКТЕРИЗАЦИЈА КОМПЛЕКСА ПАЛАДИЈУМА(II) СА ГЛИЦИНСКИМ КУМАРИНСКИМ ДЕРИВАТИМА

ДАНИЈЕЛА Љ. СТОЈКОВИЋ[1], ALESSIA BACCHI[2], DAVIDE CAPUCCI[2], МИЛИЦА Р. МИЛЕНКОВИЋ[3], БОЖИДАР ЧОБЕЉИЋ[3], СРЕЋКО Р. ТРИФУНОВИЋ[1], КАТАРИНА АНЂЕЛКОВИЋ[3], ВЕРИЦА В. ЈЕВТИЋ[1], НЕНАД ВУКОВИЋ, МИЛЕНА ВУКИЋ[1] и ДУШАН СЛАДИЋ[3]

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Синтетисан је комплекс паладијума(II) са метил-2-([1-{2,4-диоксохроман-3-илиден}етил]амино)ацетатом. Структуре како лиганда тако и комплекса паладијума(II) одређене су елементалном анализом, IC и NMR спектроскопијом. Прекристализација комплекса паладијума(II) из смеше DMF/вода резултује у његовој хидролизи и формирању комплекса диметиламин-(2-[{1-(2,4-диоксохроман-3-илиден)етил}амино]ацетато)--паладијум(II), чија структура је одређена елементалном анализом, IC, ^{1}H и ^{13}C-NMR спектроскопијом, као и рендгенском структурном анализом.

(Примљено 15. септембра, ревидирано 25. септембра, прихваћено 27. септембра 2016)

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