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Synthesis of Air Stable Fused Bicyclic Δ^4-1,2,4-oxadiazoline Platinum(II) Complexes *via* [2+3] Cycloadditions

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The reaction of *trans*-[$PtCl_2(NCR)_2$] [$R^1 = CH_2CO_2Me$ (**1a**), $R^2 = CH_2Cl$ (**1b**)] with pyrroline *N*-oxide $^-O^+\underline{N}$=$CHCH_2CH_2\underline{C}Me_2$ (**2**) furnishes, *via* [2+3] cycloaddition, new fused bicyclic Δ^4-1,2,4-oxadiazoline platinum(II) complexes *trans*-[$PtCl_2\{\underline{N}$=$C(R)O\underline{N}C(H)CH_2CH_2\underline{C}Me_2\}_2$] ($R^1 = CH_2CO_2Me$ (**3a**), $R^2 = CH_2Cl$ (**3b**)). Compounds **3a** and **3b** were refluxed in CH_2Cl_2 to afford the derived ketoimine platinum(II) complexes *trans*-[$PtCl_2\{N(C(=O)(R))=\underline{C}CH_2CH_2C(Me_2)\underline{N}H\}_2$] ($R^1 = CH_2CO_2Me$ (**4a**), $R^2 = CH_2Cl$ (**4b**)), respectively, as a result of the N-O bond cleavage of the oxadiazoline ring in compound **3**. All the platinum complexes were characterized by IR, ^1H and ^{13}C NMR spectroscopies, ESI^+-MS and elemental analyses.

Keywords: Nitriles, Nitrones, Cycloadditions, Oxadiazolines, N-O bond cleavage.

INTRODUCTION

Platinum-based compounds are important drugs for the treatment of cancer diseases. The three approved platinum based complexes *i.e., cis*-platin, carboplatin and oxaliplatin play a major role in cancer chemotherapy[1-3]. Cisplatin is one of the most successful anticancer drugs used for the therapeutic management of different solid tumors such as epithelial ovarian cancer, testicular cancers, head and neck cancers[4-6]. Nevertheless, its clinical use is limited by severe side effects such as nephrotoxicity, ototoxicity, neurotoxicity[7,8]. The carboplatin *cis*-diamine(1,1-cyclobutanedicarboxylato)-platinum(II) and oxaliplatin (*trans*-R,R-cyclohexane-1,2-diamine)oxalato-platinum(II) which are less toxic than *cis*-platin have found wide application worldwide as they have improved safety profile. *cis*-Platin and carboplatin are frequently used in combination chemotherapy and their antitumor activity contributed significantly to the improvement in survival rates for patients with ovarian and testicular cancers when they were first introduced into the clinic. More recently, the platinum analogue oxaliplatin has been developed and is now licensed for use in metastatic colon cancer in the US[9].

There is continuing interest in the development of new platinum complexes that are less toxic and have a broader spectrum of activity. Variations in the nature of the ligand can have a significant effect on the activity and toxicity of these complexes. Several platinum complexes with *N*-heterocyclic ligands such as imidazole, thiazole, benzimidazole, benzoxazole and benzothiazole have been reported[10-19]. Some of these platinum complexes showed significant cytotoxicity[10,11,14-19]. Recently, we reported that the ketoimine platinum(II) complex is an antiproliferative agent with potential to be used against cancer cells[20].

On other hand, oxadiazolines represent an important class of heterocycles which, although known for over a century, are rather limited in number. In recent years, these heterocycles have drawn greater attention due to their promising biological activities[21]. The platinum(II)-assisted 1,3-dipolar cycloaddition of nitrones to organonitriles is one of the most important routes for the synthesis of Δ^4-1,2,4-oxadiazoline platinum(II) compounds[22].

In the present work, the synthesis and characterization of the new fused bicyclic Δ^4-1,2,4-oxadiazoline platinum(II) complexes (**3a** and **3b**) were investigated. Moreover, **3a** and **3b** were converted, under heating, to the derived ketoimine platinum(II) complexes **4a** and **4b**, respectively.

EXPERIMENTAL

The organonitrile complexes *trans*-[$PtCl_2(NCR)_2$] ($R^1 = CH_2CO_2Me$ (**1a**), $R^2 = CH_2Cl$ (**1b**)) were prepared according to the published methods[22].

^1H and ^{13}C spectra (in $CDCl_3$) were measured on a Bruker Avance II 400 MHz (UltraShield™ Magnet) spectrometer at ambient temperature. ^1H and ^{13}C chemical shifts (δ) are expressed in ppm relative to TMS. *J* values are in Hz. Infrared spectra

(4000-400 cm^{-1}) were recorded on a Bio-Rad FTS 3000MX and a Jasco FT/IR-430 instrument in KBr pellets and the wavenumbers are in cm^{-1}. Electrospray mass spectra were carried out with an ion-trap instrument (Varian 500-MS LC Ion Trap Mass Spectrometer) equipped with an electrospray (ESI) ion source. The solutions in methanol were continuously introduced into the mass spectrometer source with a syringe pump at a flow rate of 10 µL/min. The drying gas temperature was maintained at 350 °C and dinitrogen was used as nebulizer gas at a pressure of 35 psi. Scanning was performed from *m/z* = 50 to 1500.

Synthesis of complexes (3a and 3b): A solution of **1a** (92.0 mg, 0.198 mmol) or **1b** (82.6 mg, 0.198 mmol) in CH_2Cl_2 (3 mL) was added to the cyclic nitrone **2** (49.3 mg, 0.436 mmol). The mixture was stirred at room temperature for 15 min and a bright yellow solution was formed. The progress of the reaction was monitored by TLC. After evaporation of the solvent *in vacuo* to dryness, the oily residue was purified by column chromatography (SiO_2/CH_2Cl_2:Et_2O (10:1)) followed by evaporation of the solvent in vacuo to give the final yellow product **3a** or **3b**, respectively.

trans-[$PtCl_2${N=C(CH_2CO_2Me)ONC(H)CH_2CH_2C Me_2}$_2$] **(3a)**. Yield: 90 %. IR (KBr, ν_{max}, cm^{-1}): 1666 (C=N), 1749 (CO_2Me). ESI^+-MS, *m/z* : 691 $[M+1]^+$. ^1H NMR ($CDCl_3$), δ: 1.14 (s, 6H, Me), 1.31 (s, 6H, Me), 1.71 (m, 4H, CH_2), 2.36 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 3.80 (s, 6H, CO_2CH_3), 3.96 (m, 2H, CH_2CO_2), 4.12 (m, 2H, CH_2CO_2), 5.55 (m, 2H, N-CH-N). ^{13}C NMR ($CDCl_3$), δ: 23.30 (Me), 27.46 (Me), 31.14 (CH_2), 34.12 (CH_2), 53.50 (CH_2CO_2), 53.72 (OMe), 71.47 (CMe_2-N), 89.94 (N-CH-N), 163.84 (C=N), 165.91 (CO_2Me). Anal. Calcd. for $C_{20}H_{32}N_4O_6PtCl_2$: C, 34.79; H, 4.67; N, 8.11; found: C, 34.85; H, 4.99; N, 7.74.

trans-[$PtCl_2${N=C(CH_2Cl)ONC(H)$CH_2CH_2CMe_2$}$_2$] (**3b**). Yield: 87 %. IR (KBr, ν_{max}, cm^{-1}): 1664 (C=N). ESI^+-MS, *m/z* : 643 $[M+1]^+$. ^1H NMR ($CDCl_3$), δ: 1.21 (s, 6H, Me), 1.49 (s, 6H, Me), 1.73 (m, 4H, CH_2), 2.37 (m, 2H, CH_2), 2.87 (m, 2H, CH_2), 4.55 (m, 2H, CH_2Cl), 4.70 (m, 2H, CH_2Cl), 5.45 (m, 2H, N-CH-N). ^{13}C NMR ($CDCl_3$), δ: 22.37 (Me), 27.13 (Me), 29.71 (CH_2), 33.71 (CH_2), 47.10 (CH_2Cl), 69.87 (CMe_2-N), 88.72 (N-CH-N), 165.93 (C=N). Anal. Calcd. for $C_{16}H_{26}N_4O_2PtCl_4$: C, 29.87; H, 4.07; N, 8.71; found: C, 29.55; H, 4.17; N, 8.45.

Synthesis of complexes (4a and 4b): A solution of **3a** (80 mg, 0.116 mmol) or **3b** (74.6 mg, 0.116 mmol) in CH_2Cl_2 (3 mL) was refluxed for 3 days. The solvent was then removed in vacuo and the resulting solid was washed with three 10 mL portions of diethyl ether and dried under air to give the final ketoimine compound **4a** or **4b**, respectively, in excellent yield.

trans-[$PtCl_2${N(C(=O)(CH_2CO_2Me))=CCH$_2$CH$_2$C(Me_2)NH}$_2$] (**4a**). Yield: 89 %. m.p.: 217 °C. IR (KBr, ν_{max}, cm^{-1}): 1574 (C=N), 1673 (NC=O), 1739 (CO_2Me), 3289 (NH). ESI^+-MS, *m/z* : 691 $[M+1]^+$. ^1H NMR ($CDCl_3$), δ: 1.61 (s, 12H, Me), 1.97 (t, 4H, CH_2, $^3J_{HH}$ 7.5 Hz), 3.33 (t, 4H, CH_2, $^3J_{HH}$ 7.5 Hz), 3.61 (s, 4H, CH_2CO_2Me), 3.80 (s, 6H, CO_2Me), 10.54 (s, br, 2H, NH). ^{13}C NMR ($CDCl_3$), δ: 28.55 (Me), 33.29 (CH_2), 36.54 (CH_2), 47.87 (CH_2CO_2), 52.49 (OMe), 64.93 (CMe_2-N), 167.69 (C=N), 174.01 (CO_2Me), 178.73 (NC=O). Anal. Calcd. for $C_{20}H_{32}N_4O_6PtCl_2$: C, 34.79; H, 4.67; N, 8.11; found: C, 34.93; H, 4.83; N, 7.88.

trans-[$PtCl_2${N(C(=O)(CH_2Cl))=CCH$_2$CH$_2$C(Me_2)NH}$_2$] (**4b**). Yield: 87 %. m.p.: 233 °C. IR (KBr, ν_{max}, cm^{-1}): 1573 (N=C), 1681 (NC=O), 3275 (NH). ESI^+-MS, *m/z*: 643 $[M+1]^+$. ^1H NMR ($CDCl_3$), δ:1.45 (s, 12H, Me), 2.03 (t, 4H, CH_2, $^3J_{HH}$ = 7.5), 3.45 (t, 4H, CH_2, J_{HH} = 7.5), 5.48 (s, 4H, CH_2Cl), 10.75 (s, br, 2H, NH). ^{13}C NMR ($CDCl_3$), δ: 28.51 (CH_3), 32.79 (CH_2), 37.01 (CH_2), 45.35 (CH_2Cl), 65.75 (CMe_2-N), 173.65 (C=N), 177.41 (NC=O). Anal. Calcd. for $C_{16}H_{26}N_4O_2PtCl_4$: C, 29.87; H, 4.07; N, 8.71; found: C, 29.63; H, 4.25; N, 8.99.

RESULTS AND DISCUSSION

The new fused bicyclic Δ^4-1,2,4-oxadiazoline platinum(II) complexes *trans*-[$PtCl_2${N=C(R)ONC(H)CH_2 CH_2CMe_2}$_2$] (R^1 = CH_2CO_2Me (**3a**), R^2 = CH_2Cl (**3b**)) were synthesized, in excellent yields about 90 %, by treatment of *trans*-[$PtCl_2(NCR)_2$] (R^1 = CH_2CO_2Me (**1a**), R^2 = CH_2Cl (**1b**)) with two equivalents of the cyclic nitrone (pyrroline *N*-oxide) $^-O^+$N=CHCH_2CH_2CMe_2 (**2**) at room temperature for 15 min (**Scheme-I**, reaction a).

Nevertheless, it was reported[23] that the reaction of **1** with **2** gave the ketoimine complex as a result of the "*spontaneous*" ring opening of the non-isolated oxadiazoline platinum(II) complex intermediate. In this work, after further complementary experiments and attempts we were able to isolate the oxadiazoline complexes **3**. Hence, the reaction of **1** with **2**, at room temperature for 15 min or even for 24 h, gives the Δ^4-1,2,4-oxadiazoline platinum(II) complexes **3** as the exclusive detected products.

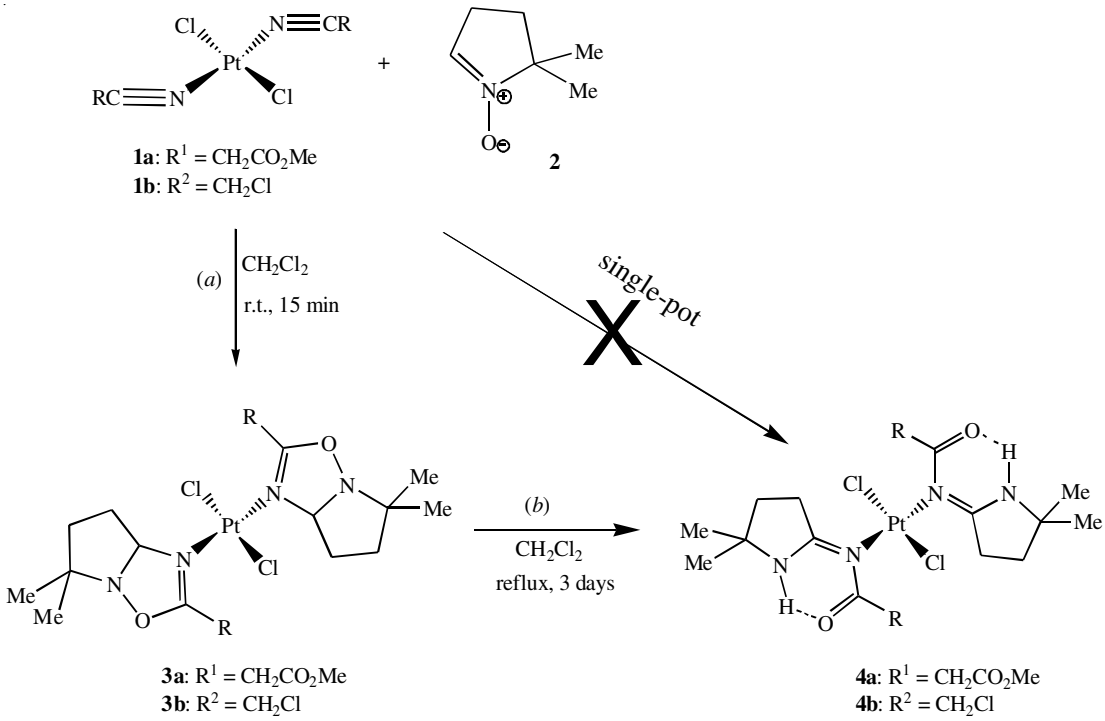
The new fused bicyclic oxadiazoline platinum(II) complexes **3** were characterized by elemental analyses, ESI^+-MS, IR, ^1H and ^{13}C NMR spectroscopies.

In contrast with the oxadiazoline platinum(II) complexes formed by reaction of acyclic nitrones with coordinated organonitriles, which exhibit two sets of signals corresponding to 1:1 diastereoisomeric mixtures[22], complexes **3** display only one set of NMR signals which indicates that the [2+3] cycloaddition reaction proceeds with high diastereoselectivity leading to the formation of a pair of enantiomers [(R,R)/(S,S)]. The structure of the cyclic nitrone **2** offers a more rigid conformation (*E*) than in the case of the acyclic ones, preventing one of the nitrone sides from the reaction, thus promoting the selectivity. A similar behaviour was noticed by us in a previous study on [2+3] cycloaddition of a cyclic nitrone to palladium(II) bound-organonitriles[24-26].

Interestingly, refluxing the Δ^4-1,2,4-oxadiazoline platinum(II) complexes **3a** and **3b**, in CH_2Cl_2 for 3 days, affords the derived ketoimine platinum(II) complexes **4a** and **4b**, respectively (**Scheme-I**, reaction b). The structure of these complexes has been confirmed by elemental analyses, ESI^+-MS, IR, ^1H and ^{13}C NMR spectroscopies.

Conclusion

For the first time, we succeeded to isolated novel symmetrical fused bicyclic Δ^4-1,2,4-oxadiazoline platinum(II) complexes **3** in a pure form and without N-O bond cleavage of the oxadiazoline rings. However, under reflux they furnish the derived ketoimine platinum(II) complexes **4** in which the N-O bond rupture is promoted by thermal heating.



Scheme-I: Synthesis of oxadiazolines (**3**) and ketoimines (**4**)

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