Nucleophilic Additions of Methanol to the Dichloropalladium(II) Complex with C-(2-Pyridyl)-N-methylnitrone

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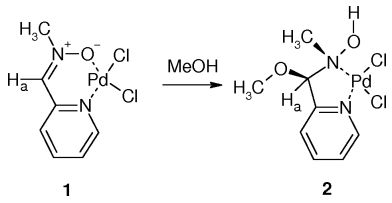
The additions of methanol to the dichloropalladium(II) complex with C-(2-pyridyl)-N-methylnitrone led to the formation of the Pd(II)-coordinated α-methoxy-α-(2-pyridyl)-N,N-dimethylhydroxylamine. It has been demonstrated that the Pd(II) complexation is essential for the stabilization of α-alkoxyhydroxylamines.

Key words: Nitrones, Palladium, α-Alkoxyhydroxylamine Complexes

Introduction

Nitrones are important starting compounds in numerous organic syntheses, in particular for 1,3-dipolar cycloadditions with unsaturated compounds and for nucleophilic additions to the azomethine-N-oxide group [1]. Both reactions can be performed in asymmetric variants and provide synthetic access to structurally diverse natural products [2]. Thus, the catalytic asymmetric 1,3-dipolar cycloadditions of nitrones and alkenes afford the enantio- or diastereomers of isoxazolidines which can be readily reduced to γ-aminoalcohols [3]. This approach was used in syntheses of 4-hydroxypyroglutamic acid and its aldehyde, which involves N-O bond reduction followed by intramolecular cyclization [4]. Nucleophilic additions of Grignard reagents to nitrones were employed in asymmetric syntheses of N-hydroxy-α-amino acids, protected N-hydroxy-α-aminoaldehydes [5] as well as α-hydroxy-β-amino acids [6]. The nitrone oxygen atom can coordinate to a metal ion or another Lewis acid, which results in a lowering of the $LUMO_{nitrone}$ energy that alleviates the 1,3-dipolar cycloadditions with electron-rich alkenes [7] and lowers the reactivity of nitrones in cycloadditions with electron-deficient alkenes [8]. Polarization of the azomethine-N-oxide group by coordination of nitrones leads to the activation of nitrones for nucleophilic additions. In spite of the apparent connection between coordinative properties of nitrones and their reactivity in organic reactions, until recently little effort has been devoted to investigations of nitrone complexes [9].

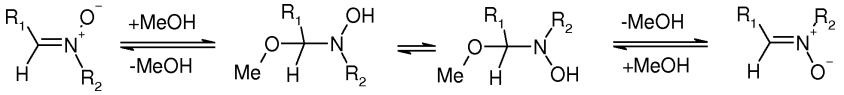


Scheme 1.

Results and Discussion

Following our studies on heteroaromatic nitrone ligands [10] we have prepared a $PdCl_2$ complex with C-(2-pyridyl)-N-methylnitrone (L). Reaction of the ligand and Na_2PdCl_4 in acetonitrile solution immediately yields a yellow microcrystalline precipitate of $Pd(L)Cl_2$ (**1**), the composition of which was established by elemental analysis and IR spectroscopy. Complex **1** is insoluble in common organic solvents, while it slowly reacts with alcohols. It was found that by treatment with methanol the compound **1** undergoes nucleophilic addition of methanol to give the α-methoxy-α-(2-pyridyl)-N,N-dimethylhydroxylamine complex **2**, as shown in Scheme 1.

The X-ray crystal structure of **2** is shown in Fig. 1. The complex **2** adopts a molecular structure with the expected planar four-fold coordination of the palla-



Scheme 2.

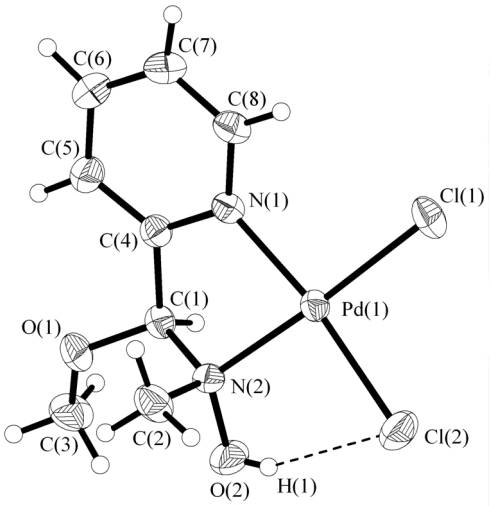


Fig. 1. Molecular structure of the palladium complex **2** with the displacement ellipsoids drawn at 50% probability level. Selected bond lengths and angles: Pd(1)-N(1) 2.016(2), Pd(1)-N(2) 2.043(2), Pd(1)-Cl(1) 2.2914(8), Pd(1)-Cl(2) 2.2964(7), N(2)-O(2) 1.438(2) Å; Cl(1)-Pd(1)-Cl(2) 92.43(3), N(1)-Pd(1)-N(2) 81.01(7)°.

dium ion. The environment of the metal centre comprises two nitrogen donors of the organic chelate (Pd(1)–N(1) 2.016(2), Pd(1)-N(2) 2.043(2) Å) and two *cis*-situated chloride ions (Pd-Cl 2.2914(8) and 2.2964(7) Å). The chelate cycle is not planar and has an envelope conformation as the hydroxylamine nitrogen atom deviates from the mean plane by 0.70 Å. Weaker intramolecular interactions are important for stabilization of the ligand conformation. Thus, the hydroxy group forms a hydrogen bond to the *cis*-chloride ligand (O(2)---Cl(2) 3.01 Å, ∠ O(2)H(1)Cl(2) 152°).

Analogous addition reactions proceed in high yield by refluxing **1** not only in methanol, but also in EtOH, PrOH, i-PrOH. Complex **1** dissolves within 3 h, and after evaporation of the alcohols the corresponding α-alkoxyhydroxylamine complexes remain as red orange solids. All the resultant compounds are stable in solid state in air and also in solutions. Our attempts to obtain adducts of this type with phenols and amines failed, and only unchanged starting materials were recovered.

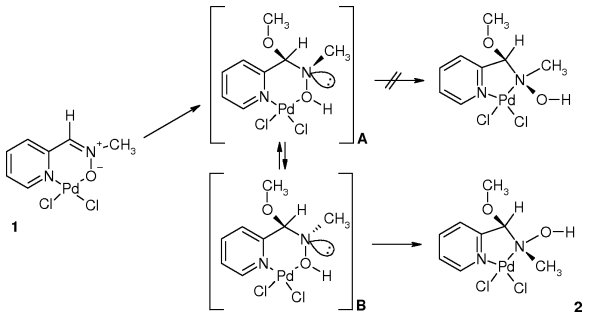
By treatment of complex **2** with ethylenediamine in acetonitrile solution only the starting nitrone L and methanol have been released. The authors of previous work [11] proposed to explain the rapid *Z-E* isomerization of C-aryl-N-alkylnitrones proceeding in CD_3OD solution in the presence of CD_3ONa in terms of reversible addition-elimination reactions of MeOH at/from the C=N double bond (Scheme 2).

The thermodynamic equilibrium of this reaction is substantially shifted to the nitrone forms, which was proved by ^{1}H NMR and UV spectroscopy data [11]. Therefore, it can be concluded, that the complexation with Pd(II) cation changes the equilibrium in favor of hydroxylamines.

The ^{1}H NMR spectrum of **2** in CD_3CN shows resonances of methoxy and hydroxy groups. There is a large upfield shift (1.6 ppm) of the signal of the proton H_a bound to the chiral carbon atom, and a downfield shift of the 3-pyridine proton signal. The ^{1}H NMR spectra of the adducts with EtOH and PrOH exhibit two different signals for the O-CH_2 diastereotopic protons.

The nitrogen atom of the hydroxylamino group coordinated to the palladium atom becomes the second chiral center in molecule **2**. Therefore, the molecule **2** and other adducts with alcohols may exist as two diastereomers having the hydroxy and alkoxy groups either in *cis* or in *trans* position. The ^{1}H NMR spectrum reveals that in the reaction outlined in Scheme 1 only a single diastereomer is formed, and the *trans*-position of oxygen containing groups can be assigned from X-ray structure data. The structure investigation of **2** in CD_3CN solution by NOE-experiments unfortunately did not give unambiguous results.

Palladium complexes with oxygen donors are not very stable, although there is a number of complexes with bidentate ligands containing along with oxygen binding group also soft donor atoms such as N, P, S, Se [12]. Since oxygen has a much lower affinity to palladium in comparison with nitrogen, we believe that the change of coordination mode from N,O-chelation in **1** to N,N-chelation in **2** is one of the driving forces that brings about the alcohol addition. The considerable increase of reactivity of the azomethine group in **1** toward the nucleophilic reagents can be explained by the electron withdrawing effect of the $PdCl_2$ moiety. Moreover, the palladium atom coordinates the nitrogen



Scheme 3.

of the hydroxylamino group in **2**, thereby stabilizing the α-methoxyhydroxylamine.

In order to explain the formation of the *trans*-diastereomer **2** we propose the mechanism outlined in Scheme 3: 1) Nucleophilic addition of methanol to the double bond of compound **1** requires the antiperiplanar alignment of the methoxy group and the lone pair of nitrogen atom, and the intermediate **A** forms initially. 2) Owing to the low inversion barrier at the tetrahedral nitrogen atom, the configuration inversion of the nitrogen atom should proceed with formation of the intermediate **B**. 3) Because of the steric repulsion between the methyl and methoxy groups, which are the most bulky substituents in the chelate ring, the intermediate **B** should be more stable than **A**. 4) Final step is the rotation around the C-N bond with the simultaneous recoordination in the N,N- (instead of the N,O-) chelation mode.

Experimental Section

Syntheses

All chemicals were commercial products of reagent grade, used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a "Mercury 400" Varian (400 MHz) spectrometer, and IR spectra were recorded on a Carl Zeiss (Jena) UR-10 spectrometer (KBr pellets, 400 – 4000 cm^{-1}).

C-(2-Pyridyl)-N-methylnitrone (L)

N-Methylhydroxylamine hydrochloride (8.770 g, 0.105 mol) was added in one portion to a stirred mixture of Na_2CO_3 (21.198 g, 0.2 mol) and pyridine-2-carbaldehyde (10.711 g, 0.1 mol) in 250 mL of CH_2Cl_2. The resulting suspension was refluxed for 3 h, cooled and filtered, and the precipitate washed twice with CH_2Cl_2. The combined filtrates were evaporated at reduced pressure. After recrystallization from cyclohexane the product was obtained as white crystals (11.16 g, 82%). – ^{1}H NMR (400.45 MHz, CD_3CN): $\delta = 3.85$ (s, 3 H, CH_3), 7.32 (ddd, $^3J_{5-4} = 7.6$ Hz, $^3J_{5-6} = 4.8$ Hz, $^4J_{5-3} = 0.8$ Hz, 1 H, 5-H), 7.76 (s, 1 H, nitrone CH), 7.82 (td, $^3J_{4-3} = ^3J_{4-5} = 7.6$ Hz, $^4J_{4-6} = 1.2$ Hz, 1 H, 4-H), 8.62 (dd, $^3J_{6-5} = 4.8$ Hz, $^4J_{6-4} = 1.2$ Hz, 1 H, 6-H), 9.04 (dd, $^3J_{3-4} = 7.6$ Hz, $^4J_{3-5} = 0.8$ Hz, 1 H, 3-H). – ^{13}C{^{1}H} NMR (100.70 MHz, CD_3CN): $\delta = 54.8$, 123.2, 124.7, 136.4, 137.3, 150.2, 150.4. – $C_7H_8N_2O$ (136.2): calcd. C 61.75, H 5.92, N 20.57; found C 61.81, H 5.93, N 20.52.

Table 1. Crystal and refinement data for palladium complex **2**.

Formula	$C_8H_{12}Cl_2N_2O_2Pd$
Formula weight	345.50
Crystal system	triclinic
Space group, Z	$P\bar{1}, 2$
Unit cell dimensions (Å, °) a, α	7.9624(9), 111.70(2)
b, β	9.0266(8), 110.30(2)
c, γ	9.611(2), 94.753(8)
V, Å^3	584.0(1)
D_{calc} (g cm^{-3})	1.965
$F(000)$	340
μ(MoK_α) cm^{-1}	20.27
$2\theta_{max}$ (deg)	53.4
Reflections measured	2560
Unique reflections (R_{int})	2412 (0.015)
Parameters refined	184
GOF on F^2	1.114
$R1, wR2$ [$I \geq 2\sigma(I)$]	0.019, 0.052
$R1, wR2$ [all data]	0.021, 0.052
Max. peak and hole, e Å^{-3}	0.64, −0.73

*Pd(L)Cl$_2$ (**1**)*

Hot acetonitrile solutions of Na_2PdCl_4 (0.294 g, 1 mmol) and C-(2-pyridyl)-N-methylnitrone (0.136 g, 1 mmol) were combined. Yellow crystals of the product were formed immediately. The precipitate was filtered off and dried. Yield 0.245 g (78%). – IR (KBr): $\nu = 1645$, 1600 (C=N), 1170 (N-O) cm^{-1}. – $C_7H_8Cl_2N_2OPd$ (313.5): calcd. C 26.82, H 2.57, N 8.94; found C 26.80, H 2.63, N 8.90.

*Compound **2** [Pd(L)Cl$_2$+CH$_3$OH]*

A mixture of **1** (0.157 g, 0.5 mmol) and 20 mL of methanol was refluxed for 3 h. During this period the starting compound dissolves slowly. After cooling, orange crystals were formed (0.126 g, 78%). – IR (KBr): $\nu = 1610$ (C=N), 1130 (N-O) cm^{-1}. – ^{1}H NMR (400.45 MHz, CD_3CN): $\delta =$ 2.90 (s, 3 H, NCH_3), 3.95 (s, 3 H, OCH_3), 6.13 (s, 1 H), 7.56 – 7.64 (m, 2 H, 3-H, 5-H), 8.16 (td, $^3J_{4-3} = ^3J_{4-5} =$ 8 Hz, $^4J_{4-6} = 1.2$ Hz, 1 H, 4-H), 8.70 (s, 1 H, OH), 8.85 (dd, $^3J_{6-5} = 5.6$ Hz, $^4J_{6-4} = 1.2$ Hz, 1 H, 6-H). – ^{13}C{^{1}H} NMR (100.70 MHz, CD_3CN): $\delta = 46.9$, 63.2, 103.2, 125.6, 127.2, 142.1, 150.0, 156.5. – $C_8H_{12}Cl_2N_2O_2Pd$ (345.5): calcd. C 27.81, H 3.50, N 8.11; found C 27.74, H 3.52, N 8.08.

Crystallography

For complex **2**, the unit cell dimensions and the intensities of the reflections were measured at r. t. using a CAD-4 Enraf Nonius diffractometer. The structure was solved by direct methods and refined in anisotropic approximation for all non-hydrogen atoms using SHELX-97 [13] (Table 1). All hydrogen atoms were located and refined isotropically.

Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC-602325. Copies of the data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[1] K. B. G. Torssell, Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis, p. 75 – 89, 129 – 255, VCH, Weinheim (1988).

[2] a) M. Frederickson, Tetrahedron **53**, 403 (1997); b) R. Pulz, S. Cicchi, A. Brandi, H. U. Reissig, Eur. J. Org. Chem, 1153 (2003); c) P. Merino, S. Franco, D. Lafuente, F. Merchan, J. Revuelta, T. Tejero, Eur. J. Org. Chem. 2877 (2003).

[3] a) D. Basso, G. Broggini, D. Passarella, T. Pilati, A. Terraneo, G. Zecchi, Tetrahedron **58**, 4445 (2002); b) M. C. Whisler, P. Beak, J. Org. Chem. **68**, 1207 (2003); c) A. Arnone, G. Broggini, D. Passarella, A. Terraneo, G. Zecchi, J. Org. Chem. **63**, 9279 (1998).

[4] a) P. Merino, S. Anoro, S. Franco, F. L. Merhan, T. Tejero, V. Tunon J. Org. Chem. **65**, 1590 (2000); b) T. Tejero, A. Dondoni, I. Rojo, F. L. Merhan, P. Merino, Tetrahedron **53**, 3301 (1997).

[5] P. Merino, E. Castillo, S. Franco, F. L. Merhan, T. Tejero, J. Org. Chem. **63**, 2371 (1998).

[6] P. Merino, E. Castillo, S. Franco, F. L. Merhan, T. Tejero, Tetrahedron **54,** 12301 (1998).

[7] a) J. P. G. Seerden, M. M. M. Boeren, H. W. Scheeren, Tetrahedron **53**, 11843 (1997); b) J. P. G. Seerden, A. W. A. Scholte op Reimer, H. W. Scheeren, Tetrahedron Lett. **35**, 4419 (1994).

[8] a) J. Tanaka, S. Kanemasa, Tetrahedron **57**, 899 (2001); b) S. Kanemasa, N. Ueno, M. Shirahase, Tetrahedron Lett. **43**, 657 (2002).

[9] a) F. A. Villamena, M. H. Dickman, De L. R. Crist, Inorg. Chem. **37**, 1446 (1998); b) P. Merino, S. Anoro, E. Cerrada, M. Laguna, A. Moreno, T. Tejero, Molecules **6**, 208 (2001).

[10] a) E. G. Petkova, K. V. Domasevitch, M. V. Gorichko, R. D. Lampeka, V. Ya. Zub, Z. Naturforsch. **56b**, 1264 (2001); b) E. G. Petkova, R. D. Lampeka, M. V. Gorichko, K. V. Domasevitch, Polyhedron **20**, 747 (2001).

[11] M. A. Voinov, B. A. Grigorjev, Izv. Akad. Nauk, Ser. Khim. 283 (2002).

[12] a) C. A. Otter, D. A. Bardwell, S. M. Couchman, J. C. Jeffery, J. P. Maher, M. D. Ward, Polyhedron **17**, 211 (1998); b) J. Andrieu, P. Braunstein, F. Naud, R. D. Adams, J. Organomet. Chem. **601**, 43 (2000); c) M. V. Esterhuysen, R. Brull, H. G. Raubenheimer, C. Esterhuysen, G. J. Kruger, J. Organomet. Chem. **619**, 164 (2001).

[13] G. M. Sheldrick, SHELXS97 and SHELXL97, The programs for crystal structure solution and refinement. University of Göttingen, Germany (1997).