ENANTIOPURE CYCLOPALLADATED and COORDINATION COMPLEXES of (S)-4-ETHYL-2-PHENYL-2-OXAZOLINE

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Abstract

The reaction of L(-)-2-amino-1-butanol and benzonitrile in the presence of ZnCl₂ afforded (S)-4-ethyl-2-phenyl-2-oxazoline [1] in 85% yield. Direct ortho-palladation of 1 using Pd(OAc)₂ and NaOAc in AcOH provided (S,S)-di-µ-acetatobis[2-[2-(4-ethyl)oxazolinyl]phenyl-C,N]dipalladium(II) [2], which was converted in situ into the corresponding µ-chloro analog 3 using LiCl in MeOH with an overall yield of 57%. The coordination complex dichlorobis[(S)-4-ethyl-2-phenyl-2-oxazolinyl]palladium(II) [4] was obtained by the reaction of 1 with PdCl₂ in MeOH in 68% yield. Dimer 3 was converted into its mononuclear PPh₃ adduct 5 in 94% yield. The structures of complexes 3-5 were proven by NMR and IR spectroscopy.

Keywords: Cyclopalladated complexes, (S)-4-Ethyl-2-phenyl-2-oxazoline, Optical activity, Coordination complexes

Introduction

Recently, enantiopure cyclopalladated complexes (CPCs) have become of great interest in organometallic chemistry due to their numerous applications. These air and moisture stable complexes have been used as catalysts (or precatalysts) (1,2) and templates (3) in asymmetric synthesis, resolving agents for chiral compounds (4), and derivitizing agents for enantiopurity determination (5).

Our interest in optically active oxazoline-based CPCs was stimulated by reports of the corresponding metal coordination complexes being used as highly efficient catalysts (6). 2-Oxazolines can be easily synthesized from commercially available α-amino acid derivatives (7-9). In continuation of our study (10,11) into the synthesis and applications of enantiopure CPCs, we have synthesized (S)-4-ethyl-2-phenyl-2-oxazoline and its corresponding cyclopalladated and coordination complexes.

Experimental

General

Chemicals were purchased from the Aldrich Chemical Co. Inc., USA or Fischer Scientific, USA. L(-)-2-Amino-1-butanol was refluxed over CaO and then distilled. Pd(AcO)₂ was dissolved in hot benzene followed by solvent removal in vacuo. AcOH was refluxed over K₂MnO₄, dried with acetic anhydride, and then fractionally distilled. MeOH was refluxed over magnesium methoxide and distilled. Other solvents were distilled over CaH₂.

Physical Measurements

Routine ¹H-NMR and ¹³C-NMR (500 MHz and 125 MHz, respectively), DEPT, COSY, and HSQC spectra were recorded in CDCl₃ using TMS as an internal standard on a Bruker AVANCE 500 spectrometer. Spin-spin coupling constants, J, are given in Hz. IR spectra were recorded on an ATI Mattson Genesis Series FTIR. Optical rotations were measured on a Rudolph Autopol III automatic polarimeter using a 1 dm tube. Analytical TLCs were performed on Whatman precoated 250 µm plates of silica gel (F₂₅₄). Column chromatography was carried out using Natland Silica Gel 60 (230-400 mesh). Melting points were measured on a Laboratory Devices Mel-Temp apparatus and were not corrected.

Ligand Synthesis

(S)-4-Ethyl-2-phenyl-2-oxazoline [1]

Oxazoline 1 was obtained as a clear and colorless liquid in 85% yield using a procedure described for a similar oxazoline (9). The crude product was

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purified by column chromatography (3:1 hexanes-EtOAc, h = 13.5 cm, d = 7 cm). **Bp** 87 °C / 4 mm Hg; Rf 0.35 (1:3 ether-hexane); [α]_D_23^23 59°, [α]_S_89^23 68.5°, [α]_S_46^23 89.2°, [α]_A_43^23 171°, [α]_A_40^23 221° (c 0.164, CH₂Cl₂); **IR** (neat, v, cm⁻¹): 1650 s (C=O), 695 s and 780 m (CH-arom.). **1H-NMR** (δ, ppm): 1.00 (t, 3H, J = 7.4, CH₃), 1.61 (m, 1H, CH₂CH₃), 1.77 (m, 1H, CH₂CH₃), 4.05 (t, 1H, J_{AB} = 7.9, OCH₃), 4.24 (m, 1H, NCH₂Et), 4.47 (dd, 1H, J_{BA} = 8.2, J_{BX} = 9.4, OCH₃), 7.40 (m, 2H, meta-CH), 7.46 (m, 1H, para-CH), 7.95 (m, 2H, ortho-CH); **13C-NMR** (δ, ppm): 10.0 (CH₃), 28.6 (CH₂CH₃), 68.0 (NCH₂Et), 72.1 (OCH₂), 128.0 (C(1)-arom.), 128.2 (meta-CH), 128.3 (ortho-CH), 131.2 (para-CH), 163.5 (OCN).

**Preparation of Complexes**


Complex 3 was obtained as a yellow powder in 57% yield according to the procedure described for a similar complex (11). The crude product was purified using column chromatography (2:1 hexanes-CH₂Cl₂, h = 4.0 cm, d = 3.5 cm) followed by recrystallization (CH₂Cl₂/pentane). **Mp** 167-168 °C; **Rf** 0.35 (1:2 hexanes-CHCl₃); [α]_D_23^23 -137°, [α]_S_89^23 -165°, [α]_S_46^23 -210°, [α]_A_43^23 -499.6° (c 0.226, CH₂Cl₂); **IR** (thin film using CH₂Cl₂, v, cm⁻¹): 1630 s (C=O), 727 s (CH-arom.). **1H-NMR** (δ, ppm): 0.95 and 0.97 (2 overlapped t, 3H, J = 7.4, CH₃), 1.80 (m, 1H, CH₂CH₃), 2.00 (m, 1H, CH₂CH₃), 4.22 (m, 1H, NCH₂Et), 4.47 (dd, 1H, J_{AB} = 8.5, J_{AX} = 5.8, OCH₃), 4.68 (dd, 1H, J_{BA} = 8.2, J_{BX} = 17.0, OCH₃), 7.04 (m, 1H, CH(5)-arom.), 7.10 (br, t, 1H, J = 7.4, CH(4)-arom.), 7.15 (br, d, 1H, J = 7.3, CH(6)-arom.), 7.40 (two d, 1H, J = 7.7, CH(3)-arom.). **13C-NMR** (δ, ppm): 7.3 and 7.4 (CH₂), 25.8 (CH₂CH₃), 61.9 and 62.2 (NCH₂Et), 73.0 and 73.1 (OCH₂), 123.5 (C(5)-arom.), 125.0 (C(6)-arom.), 129.4 (C(2)-arom.), 130.1 and 130.2 (C(4)-arom.), 131.9 and 132.0 (C(3)-arom.), 144.5 and 144.6 (PdC(1)), 173.7 (OCN). Anal. Calc. for C₃₂H₂₄Cl₂N₂O₂Pd₂: C, 50.30; H, 5.10; N, 5.33%.


The complex was obtained as a very pale yellow solid in 94% yield according to the procedure reported for a similar phosphane adduct (11). The crude product was purified using column chromatography (CH₂Cl₂, h = 1.5 cm, d = 3.5 cm) followed by recrystallization (benzene/pentane). **Mp** 102-104 °C; **Rf** 0.71 (1:18 EtOAc-CHCl₃); [α]_D_23^23 -58.4°, [α]_S_89^23 -71.3°, [α]_S_46^23 -94.4°, [α]_A_43^23 -199° (c 0.178, CH₂Cl₂); **IR** (thin film using CH₂Cl₂, v, cm⁻¹): 1639 s (C=O), **1H-NMR** (δ, ppm): 0.92 (t, 3H, J = 7.5, CH₃), 1.83 (m, 1H, CH₂CH₃), 2.21 (m, 1H, CH₂CH₃), 4.52 (m, 2H, OCH₂), 4.69 (m, 1H, NCH₂Et), 6.43 (dd, 1H, J_{HH} = 7.7, J_{HP} = 4.8, J_{HH} = 0.5, CH(6) of C₆H₄), 6.61 (dd, 1H, J_{HH} = 7.6, J_{HH} = 1.4, CH(5) of C₆H₄), 6.91 (dd, 1H, J_{HH} = 7.4, J_{HH} = 0.8, CH(4) of C₆H₄), 7.28 (dd, 1H, J_{HH} = 7.5, J_{HH} = 1.6, CH(3) of C₆H₄), 7.36 (m, 6H, meta-CH of PPh₃), 7.43 (m, 3H, para-CH of PPh₃), 7.74 (m, 6H, ortho-CH of PPh₃). **13C-NMR** (δ, ppm): 8.8 (CH₃), 27.4 (CH₂CH₃), 63.8 (d, J_{CP} = 2.9, NCCH₃), 74.7 (d, J_{CP} = 2.9, OCH₂), 123.7 (HC(4) of C₆H₄), 126.4 (HC(3) of C₆H₄), 128.0 (d, J_{CP} = 10.9, meta-C of PPh₃), 128.3 (quat. C(2) of C₆H₄),
130.7 (d, $J_{CP} = 2.5$, para-C of PPh$_3$), 130.9 (d, $J_{CP} = 50.8$, ipso-C of PPh$_3$), 130.9 (d, $J_{CP} = 5.0$, HC(5) of C$_6$H$_4$), 135.5 (d, $J_{CP} = 11.8$, ortho-C of PPh$_3$), 138.1 (d, $J_{CP} = 11.5$, HC(6) of C$_6$H$_4$), 151.8 (PdC(1)), 175.2 (OCN). Anal. Calc. for C$_{29}$H$_{27}$ClNOPPd: C, 60.22; H, 4.71; N, 2.42. Found: C, 60.58; H, 4.64; N, 2.31%.

Results and Discussion

Preparation of the Ligand and Cyclopalladated Complexes

The ligand [I] was synthesized in 85% yield from L(-)-2-amino-1-butanol and benzonitrile in the presence of ZnCl$_2$ using a procedure reported for a similar oxazoline (9) (Scheme 1).

Cyclopalladation of 1 was carried out using Pd(OAc)$_2$ and NaOAc in AcOH (Scheme 2). The unstable dimeric complex, ($S,S$)-di-$\mu$-acetatobis[2-[2-(4-ethyl)oxazolinyl]phenyl-$C,N$]dipalladium(II) [2], formed in situ was converted into the $\mu$-Cl analog 3 using LiCl in MeOH with an overall yield of 57% (Scheme 2). A major side-product was the coordination complex 4, which was isolated in 22% yield.

Compound 4 was independently synthesized by reaction of 1 with PdCl$_2$ in MeOH in 65% yield (Scheme 3).

Cyclopalladated dimer 3 was converted to its mononuclear adduct 5 by reaction with PPh$_3$ in benzene in 91% yield (Scheme 4).

Spectral Characterization of Complexes

The presence of a Pd-C bond in complexes 3 and 5 was proven by IR and NMR data. In the IR spectra of ligand 1 and coordination complex 4, two bands corresponding to out-of-plane bending vibrations of the aromatic C-H bonds were observed (695, 780 and 688, 782 cm$^{-1}$, respectively), as expected for the phenyl groups (12). The IR spectrum of CPC 3 had only one corresponding signal, which is characteristic of ortho-substituted aromatic rings (12). In the $^1$H-NMR spectrum of 4, the integral intensities of the aromatic peaks confirmed the presence of 5 aromatic protons, whereas the spectra of CPCs 3 and 5 confirmed the presence of disubstituted aromatic rings. Analysis of $^{13}$C-NMR and DEPT-135 spectra indicated that complex 3 had two quaternary aromatic carbons, whereas 5 had three. Signals at 144.5 and 144.6 ppm in the spectrum of the two geometric isomers of 3 and the signal at 151.8 ppm in the spectrum of 5 were
assigned to the quaternary carbon of the Pd-C bond. These chemical shift values are in agreement with the NMR data previously reported for other CPCs (11).

The $^{13}$C-NMR spectra of 3 in CDCl$_3$ and CD$_2$Cl$_2$ contained two sets of signals. This suggested that the dimeric complex existed in these solutions as two geometrical isomers (syn and anti, Figure 1), as was found for some other CPCs (13,14).

Figure 1. syn- and anti-Isomers of dimeric CPCs

The presence of the Pd-N bond in complexes 3-5 was substantiated by IR spectroscopy. As expected (10,11), the C=N stretching frequencies in the spectra of 3-5 (1630, 1627, and 1639 cm$^{-1}$, respectively) were shifted to shorter wavenumbers compared to the ligand 1 (1650 cm$^{-1}$).

Conclusion

Direct cyclopalladation of oxazoline 1 using Pd(OAc)$_2$ at 52-56 °C (46 h) followed by treatment with LiCl at r.t. (24 h) provided the µ-Cl dimeric CPC 3 in 57% yield. The yield of 3 was lower than that obtained for the corresponding CPC of the sterically hindered (S)-4-tert-butyl-2-phenyl-2-oxazoline ligand (74%, r.t., 22 h) (11). This supports the hypothesis that the ease of oxazoline cyclopalladation depends on the size of the substituents: for a bulkier substituent, lower temperature and shorter reaction time is required and a higher yield is observed. This trend has also been reported for the cyclopalladation of substituted benzyl amines (15).

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References