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# A Route to 1,2,4-Oxadiazoles and Their Complexes via Platinum-Mediated 1,3-Dipolar Cycloaddition of Nitrile Oxides to Organonitriles

**Nadezhda A. Bokach,[†,‡] Anatolii V. Khripoun,[†] Vadim Yu. Kukushkin,*[,†] Matti Haukka,[§] and Armando J. L. Pombeiro*[,‡]**

*St. Petersburg State University, 198904 Stary Petergof, Russian Federation, Centro de Química Estrutural, Complexo I, Instituto Superior Técnico, Av. Rovisco Pais, 1049-001 Lisbon, Portugal, and Department of Chemistry, University of Joensuu, P.O. Box 111, FIN-80101, Joensuu, Finland*

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A significant activation of the C≡N group in organonitriles upon their coordination to a platinum(IV) center has been found in the reaction of $[PtCl_4(RCN)_2]$ (R = Me, Et, $CH_2Ph$) with the nitrile oxides 2,4,6-$R'_3C_6H_2CNO$ (R′ = Me, OMe) to give the (1,2,4-oxadiazole)platinum(IV) complexes $[PtCl_4\{N{=}C(R)ON{=}CC_6H_2R'_3\}]$ (R = Me, R′ = Me (**1**); R = Et, R′ = Me (**2**); R = Et, R′ = OMe (**3**); R = $CH_2Ph$, R′ = Me (**4**)); the [2 + 3] cycloaddition was performed under mild conditions (unless poor solubility of $[PtCl_4(RCN)_2]$ precludes the reaction) starting even from complexed acetonitrile and propionitrile, which exhibit low reactivity in the free state. The reaction between complexes **2**–**4** and 1 equiv of $Ph_3P{=}CHCO_2Me$ in $CH_2Cl_2$ leads to the appropriate platinum(II) complexes $[PtCl_2\{N{=}C(R)ON{=}CC_6H_2R'_3\}]$ (**5**–**7**); the reduction failed only in the case of **1** insofar as this complex is insoluble in the most common organic solvents. All the platinum compounds were characterized by elemental analyses, FAB mass spectrometry, and IR and $^1H$, $^{13}C\{^1H\}$, and $^{195}Pt$ NMR spectroscopies, and three of them also by X-ray crystallography. The oxadiazoles formed in the course of the metal-mediated reaction were liberated almost quantitatively from their Pt(IV) complexes by reaction of the latter (complexes **2**–**4**) with an excess of pyridine in chloroform, giving free 1,2,4-oxadiazoles and *trans*-$[PtCl_4(pyridine)_2]$; the sequence of the Pt(IV)-mediated [2 + 3] cycloaddition and the liberation opens up an alternative route for the preparation of this important class of heterocycles.

## Introduction

1,2,4-Oxadiazoles represent an important class of five-membered heterocycles, and their rich chemistry has been repeatedly reviewed over the years.[1−6] Most of these surveys indicate that more than half of the original publications concerned the biological activity of these compounds and the basic concept behind many developments is that the 1,2,4-oxadiazole ring is a hydrolysis-resisting bioisosteric alternative for an ester moiety. Some derivatives of 1,2,4-oxadiazoles have intrinsic analgesic,[7] antiinflammatory,[8] and antipicornaviral[9] properties and show high efficacy as agonists (e.g., for muscarinic,[10] adrenergic,[11] and 5-hydroxytryptamine[12]) and antagonists (e.g., for angiotensin[13] and adhesion[14]) for different receptors. Other useful applications of 1,2,4-oxadiazoles include plant protection,[15] use as liquid crystalline mesophases,[16] dyeing or printing with 1,2,4-

* Authors to whom correspondence should be addressed. E-mail: kukushkin@VK2100.spb.edu (V.Yu.K.); pombeiro@ist.utl.pt (A.J.L.P.).
† St. Petersburg State University.
‡ Instituto Superior Técnico.
§ University of Joensuu.

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oxadiazole azo dyes,[17] and use as constituents of fluorescent whiteners.[18] Many of these applications have been patented.

Known synthetic approaches[1,2,4] to 1,2,4-oxadiazoles include cyclization of *O*-acylamidooximes, *N*-acylamino ethers, and nitro compounds, oxidation of dihydrooxadiazoles, amidoximes, and oximes, and 1,3-dipolar cycloaddition of nitrile oxides to nitriles. The latter route could be one of the most advantageous owing to the easy synthetic access to (and/or commercial availability of) the starting materials, but the low activation of the nitrile triple bond renders the reaction less favorable. Thus, the 1,3-dipolar cycloaddition of nitrile oxides to nonactivated nitriles proceeds only under harsh reaction conditions when the formation of 1,2,4-oxadiazoles competes with dimerization[4,19] of unstable nitrile oxides to give furoxanes or 1,2,4-oxadiazole 4-oxides.

The activation of the C≡N group in nitriles RCN—and, consequently, their reactivity toward the cycloaddition of nitrile oxides—can be enhanced by introducing strong acceptor R groups to the nitrile carbon.[20] Another mode of the nitrile activation involves affecting the nitrile through the opposite end, i.e., by coordination to a metal center via the N atom.[20,21] The latter activation type is the least explored one, and until recently it was limited to the reaction of a ligated nitrile with azides as dipoles.[20] A few years ago, within the framework of our continuous project on reactions of metal-activated nitriles (this topic has been reviewed by two of us[20]), it was found that the platinum(IV) center in $[PtCl_4(RCN)_2]$ complexes provides sufficiently strong activation of the nitriles to assist the facile [2 + 3] cycloaddition between RCN ligands and various nitrones $(R^1)(R^2)C{=}(R^3)N^+O^-$ to achieve the first examples of $\Delta^4$-1,2,4-oxadiazoline complexes $[PtCl_4(\Delta^4\text{-}1,2,4\text{-oxadiazoline})_2]$.[22,23]

In this work, we endeavored to extend the [2 + 3] cycloaddition of complexed RCN species from nitrones to nitrile oxides. The main goals of this work are the following ones: (i) to determine whether the results disclosing the enhanced reactivity of Pt(IV)-bound nitriles are specific for dipoles of allyl anion type,[24] e.g., nitrones, or the reactions can be spread out to dipoles of the propargyl/allenyl anion type,[24] e.g., nitrile oxides; (ii) to develop a general route to 1,2,4-oxadiazoles which is based on the [2 + 3] cycloaddition between the metal-activated nitriles and nitrile oxides and to perform the synthesis under mild conditions, thus preventing the nitrile oxides from dimerizing. The achieved results, showing a very high activation of nitriles upon their ligation to the metal center, thus facilitating the [2 + 3] cycloaddition of nitrile oxides, are reported in this paper.

## Experimental Section

**Materials and Instrumentation.** Solvents were obtained from commercial sources and used as received. The complexes $[PtCl_4(RCN)_2]$[25,26] and the nitrile oxides 2,4,6-$Me_3C_6H_2CNO$ and 2,4,6-$(MeO)_3C_6H_2CNO$[27] were prepared as previously described. C, H, and N elemental analyses were carried out by the Microanalytical Service of the Instituto Superior Técnico. Melting points were determined on a Kofler table. For TLC, Merck UV 254 $SiO_2$ plates were used. Positive-ion FAB mass spectra were obtained on a Trio 2000 instrument by bombarding 3-nitrobenzyl alcohol (NBA) matrixes of the samples with 8 keV (ca. $1.28 \times 10^{15}$ J) of Xe atoms. Mass calibration for data system acquisition was achieved using CsI. Infrared spectra (4000−400 $cm^{-1}$) were recorded on a BIO-RAD FTS 3000MX instrument in KBr pellets. $^1H$, $^{13}C\{^1H\}$, and $^{195}Pt$ NMR spectra in $CDCl_3$ were measured on Varian UNITY 300 and Bruker AMX 300 spectrometers at ambient temperature. $^{195}Pt$ chemical shifts are given relative to the peak of $Na_2[PtCl_6]$


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by using aqueous $K_2[PtCl_4]$ (−1630 ppm) as a standard, and the half-height line width is given in parentheses.

**Synthetic Work. Cycloaddition of Nitrile Oxides to Ligated Nitriles.** (i) A suspension of *trans*-$[PtCl_4(MeCN)_2]$ (42 mg, 0.1 mmol) and 2,4,6-$Me_3C_6H_2CNO$ (48 mg, 0.3 mmol) in MeCN (2 mL) is vigorously stirred at room temperature for 1 day, whereupon the new precipitate formed is filtered off, washed with three 3 mL portions of $CH_2Cl_2$, and dried in air at room temperature. A similar reaction with 2,4,6-$(MeO)_3C_6H_2CNO$ results in a broad mixture of yet unidentified species. (ii) A suspension of *trans*-$[PtCl_4(EtCN)_2]$ (45 mg, 0.1 mmol) and 2,4,6-$R'_3C_6H_2CNO$ ($R' = Me$, OMe) (0.4 mmol) in $CH_2Cl_2$ (2 mL) is stirred at room temperature for 1 day, whereupon the new precipitate formed is filtered off, washed with three 3 mL portions of $CH_2Cl_2$, and dried in air at room temperature. (iii) A suspension of *trans*-$[PtCl_4(PhCH_2CN)_2]$ (57 mg, 0.1 mmol) and 2,4,6-$Me_3C_6H_2CNO$ (0.6 mmol) in $PhCH_2CN$ (0.4 mL) is stirred at room temperature for 1 day, whereupon the new precipitate formed is filtered off, washed with one 2 mL portion of toluene and two 3 mL portions of $Et_2O$, and dried in air at room temperature. A similar reaction with 2,4,6-$(MeO)_3C_6H_2CNO$ results in a broad mixture of yet unidentified species.

**$[PtCl_4\{\overline{N{=}C(Me)ON{=}CC_6H_2Me_3}\}_2]$ (1).** Yield: 10%. Anal. Calcd for $C_{24}H_{28}N_4Cl_4O_2Pt$: C, 38.88; H, 3.81; N, 7.56. Found: C, 38.92; H, 3.79; N, 7.37. FAB$^+$-MS: *m*/*z* 705 $[M - Cl]^+$, 669 $[M - 2Cl]^+$, 633 $[M - 3Cl - H]^+$, 598 $[M - 4Cl - H]^+$. IR, selected bands, $cm^{-1}$: 3080 w, 2918 w [$\nu$(C−H)], 1611 and 1560 m [$\nu$(C═N + C═C)]. $^1$H NMR: $\delta$ 6.84 (s, 2H, *m*-Ph), 3.38 (s, 3H, Me), 2.31 (s, 3H, *p*-$CH_3C_6H_2$), 2.11 (s, 6H, *o*-$CH_3C_6H_2$). The solubility of the complex is insufficient to measure both $^{13}C\{^1H\}$ and $^{195}$Pt NMR spectra.

**$[PtCl_4\{\overline{N{=}C(Et)ON{=}CC_6H_2Me_3}\}_2]$ (2).** Yield: 80%. Anal. Calcd for $C_{26}H_{32}N_4Cl_4O_2Pt$: C, 40.58; H, 4.19; N, 7.28. Found: C, 40.25; H, 4.12; N, 7.10. FAB$^+$-MS: *m*/*z* 755 $[M - HCl + Na]^+$, 732 $[M - HCl]^+$, 721 $[M - 2Cl + Na]^+$, 697 $[M - HCl - Cl]^+$, 661 $[M - 3Cl - 2H]^+$, 626 $[M - 4Cl - H]^+$. IR, selected bands, $cm^{-1}$: 2983 w, 2922 m and 2855 w [$\nu$(C−H)], 1611 and 1560 m [$\nu$(C═N + C═C)]. $^1$H NMR: $\delta$ 6.63 (s, 2H, *m*-Ph), 3.87 (quart, 7.5 Hz, 2H, Et), 1.45 (t, 7.5 Hz, 3H, Et), 2.30 (s, 3H, *p*-$CH_3$Ph), 2.10 (s, 6H, *o*-$CH_3$Ph). $^{13}C\{^1H\}$ NMR: $\delta$ 141.0 (*o*-Ar), 138.8 (*p*-Ar), 127.4 (*m*-Ar), 120.7 ($C_{ipso}$) 26.5 and 12.1 (Et), 22.7 (*o*-$CH_3C_6H_2$), 21.4 (*p*-$CH_3C_6H_2$). $^{195}$Pt NMR: $\delta$ 18 (620 Hz).

**$[PtCl_4\{\overline{N{=}C(Et)ON{=}CC_6H_2Me_3}\}_2]\cdot CHCl_3$ (3).** Yield: 60%. Anal. Calcd for $C_{26}H_{32}N_4Cl_4O_8Pt\cdot CHCl_3$: C, 32.93; H, 3.38; N, 5.69. Found: C, 33.20; H, 3.60; N, 5.80. FAB$^+$-MS: *m*/*z* 830 $[M - HCl]^+$, 795 $[M - HCl - Cl]^+$, 757 $[M - 3Cl - 2H]^+$, 722 $[M - 4Cl - H]$. IR, selected bands, $cm^{-1}$: 2940 m−w [$\nu$(C−H)], 1610 s−m and 1586 m [$\nu$(C═N + C═C)]. $^1$H NMR: $\delta$ 6.00 (s, 2H, Ph), 3.84 (s and q, 5H, *p*-$C_6H_2CH_3$ and Et), 3.68 (s, 6H, *o*-$C_6H_2$-$CH_3$), 1.45 (t, 7.5 Hz, 3H, Et). $^{13}C\{^1H\}$ NMR: $\delta$ 164.4 (*p*-Ar), 161.8 (*o*-Ar), 89.5 (*m*-Ar), 55.3 (OMe), 25.9 and 11.7 (Et). The solubility of the complex is insufficient to measure the $^{195}$Pt NMR spectrum.

**$[PtCl_4\{\overline{N{=}C(CH_2Ph)ON{=}CC_6H_2Me_3}\}_2]$ (4).** Yield: 75%. Anal. Calcd for $C_{36}H_{36}N_4Cl_4O_2Pt$: C, 48.39; H, 4.06; N, 6.27. Found: C, 48.27; H, 4.21; N, 6.09. FAB$^+$-MS: *m*/*z* 856 $[M - Cl]^+$, 821 $[M - 2Cl]^+$, 786 $[M - 3Cl - 2H]^+$, 749 $[M - 4Cl - 2H]^+$. IR, selected bands, $cm^{-1}$: 3026 w, 2923 m [$\nu$(C−H)], 1611 and 1554 m [$\nu$(C═N + C═C)]. $^1$H NMR: $\delta$ 7.35 (m, 5H, $CH_2Ph$), 6.84 (s, 2H, *m*-$C_6H_2$), 5.22 (s, 2H, $CH_2$Ph), 2.29 (s, 3H, *p*-$CH_3C_6H_2$), 2.12 (s, 6H, *o*-$CH_3C_6H_2$). $^{13}C\{^1H\}$ NMR: $\delta$ 141.0 (*o*-Ar), 127.4 (*m*-Ar), 128.0, 129.6, and 128.9, (*o*-, *m*-, and *p*-Ph$CH_2$), 38.4 ($CH_2$-Ph), 22.6 (*o*-$CH_3$Ar), 21.4 (*p*-$CH_3$Ar). The solubility of the complex is insufficient to measure the $^{195}$Pt NMR spectrum.

**Reduction of the (1,2,4-Oxadiazole)platinum(IV) Complexes.** The reduction was carried out with the carbonyl-stabilized phosphorus ylide $Ph_3P{=}CHCO_2Me$ using the method previously described,[28] and the final platinum(II) complexes were purified by column chromatography on $SiO_2$. The very low solubility of $[PtCl_4\{\overline{N{=}C(Me)ON{=}CC_6H_2Me_3}\}_2]$ in the most common organic solvents, e.g., dichloromethane, does not allow the compound to be selectively reduced.

**$[PtCl_2\{\overline{N{=}C(Et)ON{=}CC_6H_2Me_3}\}_2]$ (5).** Yield: 60−80%. Anal. Calcd for $C_{26}H_{32}N_4Cl_2O_2Pt$: C, 44.70; H, 4.62; N, 8.02. Found: C, 44.72; H, 4.61; N, 7.85. FAB$^+$-MS: *m*/*z* 699 $[M + H]^+$, 627 $[M - 2Cl]^+$. IR, selected bands, $cm^{-1}$: 2922 m−w and 2856 w [$\nu$(C−H)], 1612 m and 1576 s [$\nu$(C═N + C═C)]. $^1$H NMR, two sets of signals for each proton: $\delta$ 7.02 and 6.91 (s, 2H, *m*-Ar), 3.69 and 3.25 (quart, 7.5 Hz, 2H, Et), 2.50 and 2.39 (s, 3H, *p*-$CH_3C_6H_2$), 2.29 and 1.99 (s, 6H, *o*-$CH_3C_6H_2$), 1.68 and 1.41 (t, 7.5 Hz, 3H, Et). $^{13}C\{^1H\}$ NMR: $\delta$ 182.0 (Pt−N═C−O), 167.1 and 166.9 (N═C−N), 140.3 and 140.2 (*p*-Ar), 139.0 and 138.8 (*o*-Ar), 128.4 (*m*-Ar), 120.9 and 120.3 ($C_{ipso}$), 21.9 and 21.3 ($CH_2$ from Et), 21.5 and 21.3 (*p*-$CH_3C_6H_2$), 20.8 and 20.4 (*o*-$CH_3C_6H_2$), 9.9 and 10.0 ($CH_3$ from Et). $^{195}$Pt NMR: $\delta$ −2224 (700 Hz).

**$[PtCl_2\{\overline{N{=}C(Et)ON{=}CC_6H_2(OMe)_3}\}_2]$ (6).** Yield: 50%. Anal. Calcd for $C_{36}H_{36}N_4Cl_2O_8Pt$: C, 39.30; H, 4.06; N, 7.05. Found: C, 39.35; H, 4.09; N, 6.96. FAB$^+$-MS: *m*/*z* 817 $[M + Na]^+$, 794 $[M + H]^+$, 759 $[M - Cl - H]^+$, 722 $[M - 2Cl - H]^+$. IR, selected bands, $cm^{-1}$: 2938 m−w and 2845 w [$\nu$(C−H)], 1616 s−m and 1695 m [$\nu$(C═N + C═C)]. $^1$H NMR: $\delta$ 3.86 (s, 3H, *p*-OMe) 3.76 (s, 6H, *o*-OMe), 3.22 (quart, 7.6 Hz, 2H, Et), 1.40 (t, 7.6 Hz, 3H, Et), 6.17 (s, 2H, *m*-Ph). $^{13}C\{^1H\}$ NMR: $\delta$ 9.9 (Et), 21.2 (Et), 55.4 (*o*-$CH_3OC_6H_2$), 55.8 (*p*-$CH_3OC_6H_2$), 90.1 (*m*-Ar), 95.8 ($C_{ipso}$), 160.5 (*o*-Ar), 163.4 (N═C−N), 164.4 (*p*-Ar), 180.9 (N═C−O). $^{195}$Pt NMR: $\delta$ −2201 (850 Hz).

**$[PtCl_2\{\overline{N{=}C(CH_2Ph)ON{=}CC_6H_2Me_3}\}_2]\cdot 0.25CH_2Cl_2$ (7).** Yield: 70%. Anal. Calcd for $C_{36}H_{36}N_4Cl_4O_2Pt\cdot 0.25CH_2Cl_2$: C, 51.59; H, 4.36; N, 6.64. Found: C, 51.67; H, 4.46; N, 6.60. FAB$^+$-MS: *m*/*z* 823 $[M]^+$, 750 $[M - 2Cl - H]^+$. IR, selected bands, $cm^{-1}$: 2923 m−w and 2854 w [$\nu$(C−H)], 1611 m and 1578 s−m [$\nu$(C═N + C═C)]. $^1$H NMR: $\delta$ 2.28 and 1.99 (s, 6H, *o*-Me), 2.50 and 2.24 (s, 3H, *p*-Me), 4.86 and 4.64 (s, 2H, $CH_2$Ph), 6.93 (s, 2H, *m*-Ar), 7.43 and 7.37 (m, 5H, $CH_2Ph$). $^{13}C\{^1H\}$ NMR: $\delta$ 33.8 and 33.7 ($CH_2$Ph), 20.8 and 20.4 (*o*-$CH_3C_6H_2$), 21.5 and 21.2 (*p*-$CH_3C_6H_2$), 141.0 (*o*-Ar), 127.4 (*m*-Ar), 129.3, 129.1 and 129.0 (*o*- and *m*-Ph$CH_2$), 128.1 (*p*-Ph$CH_2$), 128.4 and 128.3 (*m*-Ar), 131.4 and 130.9 ($C_{ipso}$ from $CH_2Ph$), 120.6 and 120.3 ($C_{ipso}$ from Ar), 141.1 and 140.4 (*p*-Ar), 139.0 and 138.8 (*o*-Ar), 167.3 and 166.9 (N═C−N), 179.8 and 179.6 (N═C−O). $^{195}$Pt NMR: $\delta$ −2235 (700 Hz).

**Attempted Cycloaddition to (Nitrile)platinum(II) Complexes.** Nitrile oxide (0.2 mmol) is added to a solution of *trans*-$[PtCl_2(EtCN)_2]$ (20 mg; 0.05 mmol) in $CHCl_3$ (5 mL). The mixture is refluxed for 6−8 h, whereupon that solvent is evaporated and the residue is analyzed by $^1$H NMR and FAB-MS. Apart from unidentified products, the following ones are observed in FAB$^+$-MS: $[PtCl_2(EtCN)\{\overline{N{=}C(Et)ON{=}CC_6H_2Me_3}\}]$, *m*/*z* 536 $[M - H]^+$, 500 $[M - HCl]^+$, 465 $[M - 2Cl - H]^+$, 445 $[M - HCl -$

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EtCN]$^+$, 410 [M − 2Cl − EtCN − H]$^+$; [$PtCl_2$(EtCN){N=C(Et)-ON=C$C_6H_2$(OMe)$_3$}], *m*/*z* 608 [M − H + Na]$^+$, 584 [M − H]$^+$, 549 [M − Cl]$^+$, 514 [M − 2Cl]$^+$.

**Preparation of *trans*-[$PtCl_4${HN=C(Et)ON=C(H)$C_6H_2Me_3$}$_2$] (8).** This complex was obtained by the reaction of *trans*-[$PtCl_4$(EtCN)$_2$] and the aldoxime HON=CH($C_6H_2Me_3$) in accord with the published method for related complexes.[25] Yield: 92%. Anal. Calcd for $C_{26}H_{34}N_4Cl_4O_2Pt$: C, 40.37; H, 4.69; N, 7.24. Found: C, 40.08; H, 4.73; N, 6.96. FAB$^+$-MS: *m*/*z* 665 [M − 3Cl]$^+$, 630 [M − 4HCl]$^+$. IR, selected bands, cm$^{-1}$: 3280 m [$\nu$(N−H)], 2978 w, 2921 w [$\nu$(C−H)], 1657 and 1642 [$\nu$(C=N)]. $^1$H NMR: $\delta$ 8.87 (s, 1H, CH), 8.74 (s, br, 1H, NH), 6.94 (s, 2H, *m*-Ar), 3.26 (quart, 7.6 Hz, 2H, $CH_2$ from Et), 2.49 (s, 6H, *o*-$CH_3C_6H_2$), 2.31 (s, 3H, *p*-$CH_3C_6H_2$), 1.36 (t, 7.6 Hz, 3H, $CH_3$ from Et). $^{13}$C{$^1$H} NMR: $\delta$ 177.0 (C=N), 15.9 (CH), 142.4 (*p*-Ar), 139.9 (*o*-Ar), 130.3 (*m*-Ar), 122.8 ($C_{ipso}$), 24.9 ($CH_2$ from Et), 22.2 (*o*-$CH_3C_6H_2$), 21.3 (*p*-$CH_3C_6H_2$), 10.6 ($CH_3$ from Et). $^{195}$Pt NMR: $\delta$ −171.7 (660 Hz).

**Attempted Ligand Oxidation of 8.** Reactions of **8** with $Cl_2$ in $CH_2Cl_2$ (20 min) or with $H_2O_2$ in $CDCl_3$ (1 day), at room temperature, afford a mixture of unidentified products.

**Liberation of 1,2,4-Oxadiazoles.** One drop of pyridine is added to a suspension of **2**−**4** (20 mg) in $CHCl_3$ (0.5−1 mL) and the mixture left to stand at 40 °C for 2 days, whereupon the yellow precipitate formed is filtered off and 1,2,4-oxadiazole from the filtrate is purified by column chromatography on $SiO_2$ (silica gel 70−230 mesh, 60 Å, Aldrich; eluent $CH_2Cl_2$, first fraction).

**N=C(Et)ON=C$C_6H_2Me_3$ (9).** EI-MS: *m*/*z* 216 [M]$^+$, 161 [M − EtCN]$^+$. IR, selected bands, cm$^{-1}$: 2961 w, 2922 m−w and 2854 w [$\nu$(C−H)], 1612 m and 1577 s−m [$\nu$(C=N + C=C)]. $^1$H NMR: $\delta$ 1.44 (t, 7.8 Hz, 3H, Et), 2.98 (quart, 7.8 Hz, 2H, Et), 6.91 (s, 2H, *m*-Ar), 2.29 (s, 3H, *p*-$CH_3C_6H_2$), 2.15 (s, 6H, *o*-$CH_3C_6H_2$). $^{13}$C{$^1$H} NMR: $\delta$ 180.4 (O−C=N), 168.2 (N−C=N), 139.6 (*p*-Ar), 137.7 (*o*-Ar), 21.2 (*p*-$MeC_6H_2$), 20.0 (*o*-$MeC_6H_2$), 20.0 and 10.8 (Et).

**N=C(Et)ON=C$C_6H_2(OMe)_3$ (10).** EI-MS: *m*/*z* 264 [M]$^+$, 233 [M − MeO]$^+$, 235 [M − Et]$^+$, 207 [M − EtCN]$^+$, 209 [M − EtCO]$^+$. IR, selected bands, cm$^{-1}$: 2961 m−w [$\nu$(C−H)], 1620 s−m and 1583 s−m [$\nu$(C=N + C=C)]. $^1$H NMR: $\delta$ 6.15 (s, 2H, *m*-Ar), 3.83 (s, 3H, *p*-$CH_3C_6H_2$), 3.74 (s, 6H, *o*-$CH_3C_6H_2$), 2.96 (quart, 7.6 Hz, 2H, Et), 1.43 (t, 7.6 Hz, 3H, Et). $^{13}$C{$^1$H} NMR: $\delta$ 10.6 (Et), 20.3 (Et), 55.9 (*o*-$CH_3O$), 55.4 (*p*-$CH_3O$), 90.6 (*m*-Ar), 163.1 (*p*-Ar), 160.1 (*o*-Ar), 163.9 (N=C−N), 180.0 (N=C−O).

**N=C($CH_2$Ph)ON=C$C_6H_2Me_3$ (11).** EI-MS: *m*/*z* 278 [M]$^+$, 263 [M − Me]$^+$, 248 [M − 2Me]$^+$, 187 [M − $CH_2$Ph]$^+$, 160 [M − $PhCH_2CN$]$^+$, 161 [M − $PhCH_2CN$ − H]$^+$, 91 [$PhCH_2$]$^+$. IR, selected bands, cm$^{-1}$: 2961 w, 2922 m−w and 2854 w [$\nu$(C−H)], 1612 m and 1577 s−m [$\nu$(C=N + C=C)]. $^1$H NMR: $\delta$ 7.3 (m, $CH_2$*Ph*), 6.90 (s, *m*-Ar), 4.30 (s, *CH*$_2$Ph), 2.28 (s, *p*-$CH_3C_6H_2$), 2.13 (s, *o*-$CH_3C_6H_2$). $^{13}$C{$^1$H} NMR: $\delta$ 20.0 (*o*-Ar), 21.1 (*p*-Ar), 33.0 (*CH*$_2$Ph), 128.8 and 128.9 ($CH_2$*Ph*), 137.7 (*o*-Ar).

**X-ray Structure Determinations.** The X-ray diffraction data were collected with a Nonius KappaCCD diffractometer using Mo K$\alpha$ radiation ($\lambda$ = 0.71073 Å). The Denzo-Scalepack[29] program package was used for cell refinements and data reduction. The structures **6** and **8** were solved by direct methods using the SHELXS97 and SIR97 programs and the WinGX graphical user interface.[30−32] Structure **2** was solved by the Patterson method using the DIRDIF-99 program.[33] A multiscan absorption correction based on equivalent reflections (XPREP in SHELXTL v. 5.1)[34] was applied to all data ($T_{min}$/$T_{max}$ values were 0.21680/0.31796, 0.11832/0.16567, and 0.22291/0.30662 for **2**, **6**, and **8**, respectively). Structural refinements were carried out with SHELXL97.[35] In structure **8**, NH hydrogens were located from the difference Fourier map. All other hydrogens were placed in idealized positions. The NH hydrogen in **8** was refined isotropically, while other hydrogens were constrained to ride on their parent atom. The crystallographic data are summarized in Table 1. Selected bond lengths and angles are shown in Table 2 and in Figure 1.

**Table 1.** Crystal Data for Compounds **2**, **6**, and **8**

| | **2** | **5** | **8** |
|---|---|---|---|
| empirical formula | $C_{26}H_{36}Cl_4N_4O_2Pt$ | $C_{26}H_{32}Cl_4N_4O_2Pt$ | $C_{26}H_{32}Cl_2N_4O_8Pt$ |
| fw | 773.48 | 769.45 | 794.55 |
| Temp (K) | 150(2) | 120(2) | 150(2) |
| $\lambda$ (Å) | 0.71073 | 0.71073 | 0.71073 |
| cryst syst | monoclinic | triclinic | monoclinic |
| space group | $P2_1/c$ | $P\bar{1}$ | $P2_1/n$ |
| *a* (Å) | 10.0441(2) | 6.7156(4) | 16.3688(3) |
| *b* (Å) | 16.6046(3) | 10.0296(6) | 7.6474(2) |
| *c* (Å) | 9.2969(2) | 11.9766(8) | 22.9269(6) |
| $\alpha$ (deg) | 90 | 65.932(3) | 90 |
| $\beta$ (deg) | 100.4701(8) | 82.563(3) | 91.6665(7) |
| $\gamma$ (deg) | 90 | 76.640(4) | 90 |
| *V* (Å$^3$) | 1524.70(5) | 716.05(8) | 2868.75(12) |
| *Z* | 2 | 1 | 4 |
| $\rho_{calcd}$ (Mg/m$^3$) | 1.685 | 1.784 | 1.840 |
| $\mu$(Mo K$\alpha$) (mm$^{-1}$) | 4.982 | 5.303 | 5.133 |
| R1[a] ($I \geq 2\sigma$) | 0.0250 | 0.0357 | 0.0321 |
| wR2[b] ($I \geq 2\sigma$) | 0.0566 | 0.0765 | 0.0692 |

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

**Table 2.** Selected Bond Lengths (Å) and Angles (deg) for Structures **2** and **6**[a]

| | **2** | **6**(A) | **6**(B) |
|---|---|---|---|
| Pt(1)−Cl(1) | 2.3176(12) | 2.2955(14) | |
| Pt(1)−Cl(2) | 2.3150(13) | 2.3057(13) | |
| Pt(1)−N(1) | 2.078(4) | 2.015(4) | 2.021(4) |
| N(1)−C(1) | 1.320(7) | 1.320(6) | 1.311(6) |
| C(1)−O(1) | 1.329(6) | 1.333(6) | 1.344(6) |
| O(1)−N(2) | 1.422(6) | 1.439(6) | 1.420(5) |
| N(2)−C(4) | 1.304(7) | 1.292(7) | 1.288(7) |
| Cl(1)−Pt(1)−Cl(2) | 85.55(5) | 179.13(5) | |
| Cl(1)−Pt(1)−N(1) | 88.58(12) | 89.25(12) | 88.99(12) |
| Cl(2)−Pt(1)−N(1) | 91.96(12) | 91.00(12) | 90.79(12) |
| N(1)−C(1)−O(1) | 110.2(4) | 110.8(5) | 110.5(5) |
| C(1)−O(1)−N(2) | 108.4(4) | 107.5(4) | 107.6(4) |
| O(1)−N(2)−C(4) | 104.5(4) | 103.3(4) | 104.3(4) |
| N(2)−C(4)−N(1) | 111.3(5) | 113.7(5) | 112.8(5) |

[a] The unequivalent halves of molecule **6** are denoted as **6**(A) and **6**(B).

## Results and Discussion

**Cycloaddition Reaction.** Despite the versatile organic chemistry of nitrile oxides, as reflected in a large number of

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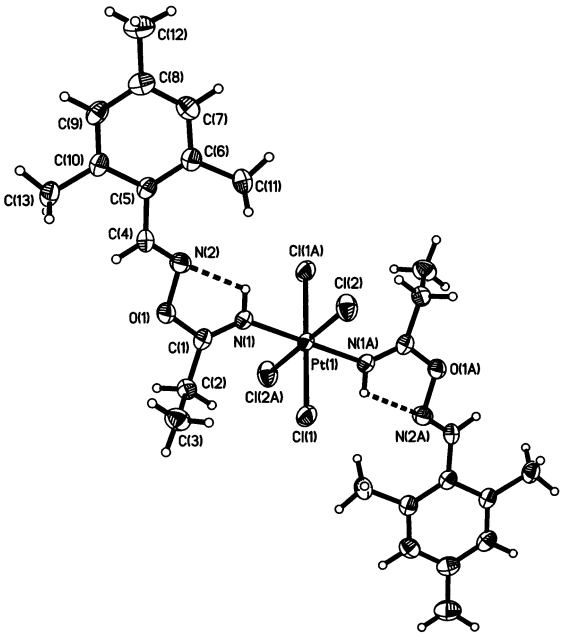
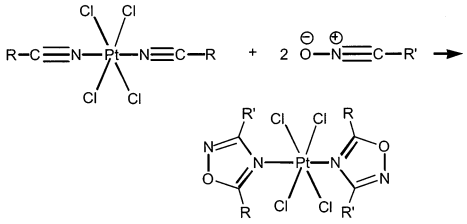



**Figure 1.** Molecular structure of **8**. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): Pt(1)−N(1) 2.023(3), Pt(1)−Cl(2) 2.3162(9), Pt(1)−Cl(1) 2.3198(8), N(1)−C(1) 1.273(4), C(1)−C(2) 1.482(5), C(1)−O(1) 1.357(4), O(1)−N(2) 1.449(4), N(2)−C(4) 1.268(4); Cl(1)−Pt(1)−Cl(2) 89.22(4), Cl(1)−Pt(1)−N(1) 93.66(9), Cl(2)−Pt(1)−N(1) 86.26(8), N(1)−C(1)−C(2) 128.9(3), N(1)−C(1)−O(1) 120.1(3), C(1)−O(1)−N(2) 112.3(2), O(1)−N(2)−C(4) 108.7(3). Hydrogen bond parameters: N(1)−H(1) 0.89(4), H(1)···N(2) 2.07, N(1)···N(2) 2.557(4), N(1)−H(1)···N(2) 114(3).

reviews[36−38] and books,[19] their coordination chemistry is still poor, and known examples include deoxygenation of nitrile oxides with $Fe(CO)_5$[39] or Pt(0)-bound phosphines[40] and the reaction of isocyanide cobalt complexes with a nitrile oxide, which leads to the formation of carbamoyl cobalt compounds.[41] In addition, a few publications concern the dipolar cycloaddition of nitrile oxides to coordinated ligands by reactions with metal carbonyls[42,43] and multiple bonds in [W]−P═C[44] and also the cycloaddition to remote C═C and C≡C bonds which are not ligated to a metal center.[45−49] To the best of our knowledge, 1,3-dipolar cycloaddition of nitrile oxides to coordinated nitriles has not yet been investigated.

**Scheme 1.** 1,3-Dipolar Cycloaddition of Nitrile Oxides



As dipolarophiles for this study we addressed the platinum(IV) complexes $[PtCl_4(RCN)_2]$ (R = Me, Et, $CH_2Ph$) because it has been proven by our previous works that the RCN ligands are highly activated toward the addition of nucleophiles such as oximes,[25,50,51] dione monoximes,[52] *vic*-dioximes,[53] hydroxylamines,[54] hydroxamic acids,[55] alcohols,[56] and imines and sulfimides[57] and they are also quite reactive in 1,3-dipolar cycloaddition of nitrones.[22,23] Two relatively stable aryl nitrile oxides, i.e., 2,4,6-$Me_3C_6H_2CNO$ and 2,4,6-$(MeO)_3C_6H_2CNO$,[27] have been chosen as dipoles. The reaction between $[PtCl_4(EtCN)_2]$, exhibiting moderate solubility in $CH_2Cl_2$, and the nitrile oxides in a molar ratio of 1:4 proceeds smoothly in a suspension at room temperature and is complete after 1 day (Scheme 1), and the final products were isolated in good yields. The reaction with the two other nitrile complexes $[PtCl_4(RCN)_2]$ (R = Me, $PhCH_2$) is hampered by their very low solubility even in the appropriate neat nitriles, and we were able to obtain (1,2,4-oxadiazole)-platinum complexes **1** and **4** only with the more stable nitrile oxide, i.e., 2,4,6-$Me_3C_6H_2CNO$, while in the case of 2,4,6-$(MeO)_3C_6H_2CNO$ gradual decomposition of the latter is faster than the overall process comprising the dissolution of the starting material and the cycloaddition.

To get an estimate of the effect of the metal center on the cycloaddition, the reaction between 2,4,6-$Me_3C_6H_2CNO$ (0.01 mmol) and $[PtCl_4(EtCN)_2]$ (0.005 mmol) or EtCN (0.01 mmol) has been investigated in $CDCl_3$ *solution* (1.5 mL) at 50 °C. It was found that signals from the cycloaddition products appear in the spectra after 20 min and 18 h, correspondingly. These data explicitly show the activation effect of the metal center and indicate that the cycloaddition

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can be performed under mild conditions starting even from complexed acetonitrile and propionitrile, which exhibit low reactivity in the free state.

We also tried to perform the cycloaddition of 2,4,6-$Me_3C_6H_2CNO$ to nitriles in the platinum(II) complex $[PtCl_2(EtCN)_2]$ upon prolonged reflux of these reagents in $CHCl_3$ solution, whereupon the solvent was evaporated and the residue was analyzed by $^1H$ NMR and FAB-MS. New signals were observed in $^1H$ NMR spectra, but their intensity is much lower than that of the signals from starting Pt(II) complex and products from the degradation of nitrile oxide, and they are close to the detection limit. However, peaks from products of the cycloaddition to only one ligated nitrile, i.e., $[PtCl_2(EtCN)\{\overline{N{=}C(Et)ON{=}CC_6H_2Me_3}\}]$ and $[PtCl_2(EtCN)\{\overline{N{=}C(Et)ON{=}CC_6H_2(OMe)_3}\}]$, were observed in $FAB^+$ mass spectra.

We also attempted to develop another route to the (1,2,4-oxadiazole)platinum(IV) complexes as follows: (i) coupling between EtCN in *trans*-$[PtCl_4(EtCN)_2]$ and the oxime $HON{=}C(H)C_6H_2Me_3$ to give **8** (for the X-ray structure see Figure 1, and for characterization see the Experimental Section), (ii) the Piloty reaction[58] of **8** with $Cl_2$, hoping to furnish $[PtCl_4\{HN{=}C(Et)ON{=}C(Cl)C_6H_2Me_3\}_2]$ followed by dehydrochlorination (similar to that observed in the case of halo alcohols[59]) to yield $[PtCl_4(1,2,4\text{-oxadiazole})_2]$. However, the chlorination of **8** brings about overall degradation of the complex, and the Piloty product was not isolated.

**Reduction of the (1,2,4-Oxadiazole)platinum(IV) Complexes to the Corresponding (1,2,4-Oxadiazole)platinum-(II) Complexes.** The reaction between complexes **2**−**4** and 1 equiv of $Ph_3P{=}CHCO_2Me$ proceeds under mild conditions (50 °C, 24 h) in $CH_2Cl_2$ to give the reduction product along with various (partially identified[28]) phosphorus-containing species; the latter are retained on $SiO_2$ upon purification by column chromatography, while the former come out in the first fraction. The reduction failed only in the case of **1** insofar as this complex is insoluble in the most common organic solvents. The Pt(II) compounds **5**−**7** were characterized by elemental analyses, FAB mass spectrometry, and IR and $^1H$, $^{13}C\{^1H\}$, and $^{195}Pt$ NMR spectroscopies, and **6** was also characterized by X-ray crystallography (see later). General features of the IR and $^1H$ and $^{13}C\{^1H\}$ NMR spectra of the corresponding Pt(II) and Pt(IV) complexes are similar. The most significant difference between the two types of complexes was detected for **2** and **5** in their $^{195}Pt$ NMR spectra, which show the shift of the Pt(IV) signal from 18 (**2**) to −2224 (**5**) ppm. Thus, the (1,2,4-oxadiazole)platinum-(II) complexes which could not be prepared by the cycloaddition between $[PtCl_2(RCN)_2]$ and nitrile oxides were prepared by the alternative route via reduction of the Pt(IV) precursors. The obtained $[PtCl_2(1,2,4\text{-oxadiazole})_2]$ complexes were employed in attempted liberation of the heterocycles (see later).

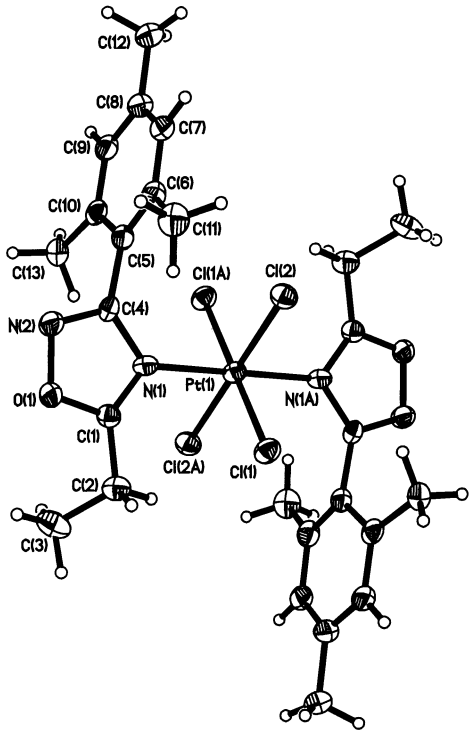


**Figure 2.** Molecular structure of **2**. Thermal ellipsoids are drawn at the 50% probability level.

**Characterization of the (1,2,4-Oxadiazole)platinum Complexes.** The structures of the platinum(IV) **2** (Figure 2) and the platinum(II) **6** complexes (Figure 3) were determined by X-ray diffraction. The coordination polyhedra of the complexes are a slightly distorted octahedron and a square plane, correspondingly. The Pt−Cl bond lengths are normal.[25]

The crystallographic data indicate the presence of two 1,2,4-oxadiazole ligands bound to the Pt atom via their $N^4$ atoms. To the best of our knowledge, despite the wealth of structural chemistry of uncoordinated 1,2,4-oxadiazoles,[60] only three structures of complexed species are known, i.e., Sn(IV),[61] Fe(II),[62] and Ni(II) complexes.[62] The structures

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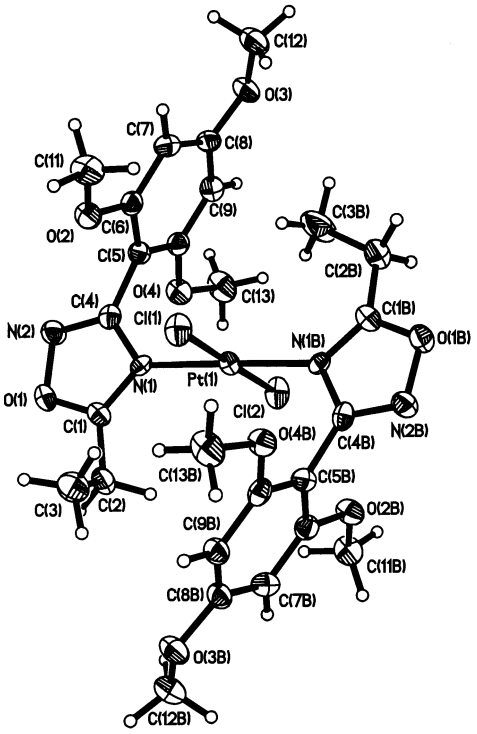
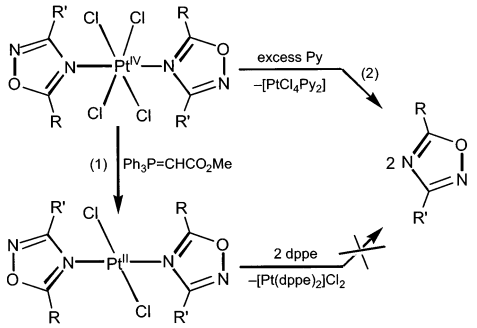



**Figure 3.** Molecular structure of **5**. Thermal ellipsoids are drawn at the 50% probability level.

reported here are the first examples of (1,2,4-oxadiazole)-platinum compounds. The geometrical parameters of the ring are almost unaffected by ligation of the heterocycles to the metal centers or by a change of the oxidation state of the Pt center (Table 2). Indeed, all bond lengths and angles in the cycle of coordinated 1,2,4-oxadiazoles within $3\sigma$ correspond to those in the purely organic species.[60]

In addition to the X-ray structural data, formulation of complexes **1**−**4** was supported by satisfactory C, H, and N elemental analyses and agreeable FAB mass spectrometry data, and the complexes were also characterized by IR and $^1$H, $^{13}$C{$^1$H}, and $^{195}$Pt NMR spectroscopies. The IR spectra of the platinum(IV) complexes **1**−**4** and the platinum(II) complexes **5**−**7** display two bands of medium intensity, $\nu$(C═N and C═C from aromatic and heteroaromatic rings), which emerge in the ranges of 1611−1616 and 1550−1580 cm$^{-1}$, and these values for the coordinated heterocycles are in good agreement with those for the corresponding free 1,2,4-oxadiazoles. In the $^1$H NMR spectra of **1**−**4**, signals of the alkyl group derived from the parent complexed nitrile and of the aromatic and alkyl groups from the parent nitrile oxide were detected in a 1:1 ratio, which corresponds to the cycloaddition of the nitrile oxide to both the coordinated nitriles. Comparison of the $^1$H NMR spectra of **1**−**4** with the spectra of the starting nitrile complexes [$PtCl_4(RCN)_2$] shows a lower field shift (ca. 0.4−0.5 ppm) of the alkyl group R in the products. Two sets of signals for each proton and carbon in both $^1$H and $^{13}$C{$^1$H} NMR spectra were observed for the two Pt(II) complexes, i.e., **5** and **7**, and we attribute this to nonequivalence of the bulky ligands. Because of the low solubility of the Pt(IV) compounds **1**−**4** in the most common organic solvents, we were unable to obtain their complete spectra. However, the platinum(II) compounds **5**−**7** exhibit higher solubility, and signals of carbons from the heteroaromatic rings were detected. For the three compounds, the $^{13}$C signals of the group N═C−O lie in the range 179.6−182.0 ppm and the signals of N═C−N in the range 163.4−167.3 ppm. For the uncoordinated 1,2,4-oxadiazoles these signals appear at 180.0 and 180.4 (N═C−O) and 163.9 and 168.2 (N═C−N) ppm, which are very close to the coordinated ones. All complexes exhibit only one signal in the $^{195}$Pt NMR spectra.

**Scheme 2.** Reduction of the Platinum(IV) Oxadiazole Complexes to the Platinum(II) Oxadiazole Complexes and Liberation of 1,2,4-Oxadiazoles from the Former Complexes




**Liberation of 1,2,4-Oxadiazoles from the Platinum Complexes.** The heterocycles formed in the course of the metal-mediated reaction were liberated almost quantitatively from their Pt(IV) complexes. The method is based on the reaction of the platinum(IV) complexes **2**−**4** with an excess of pyridine in chloroform, giving free 1,2,4-oxadiazoles in solution and a precipitate of the well-known *trans*-[$PtCl_4$-(pyridine)$_2$][63] (Scheme 2).

The latter complex is separated from the reaction mixture by filtration, whereupon the filtrate is evaporated to dryness to give the pure 1,2,4-oxadiazoles **9**−**11**. Compound **1** exhibits very low solubility in the most common solvents, and the oxadiazole was not released even on prolonged heating with pyridine. Moreover, the endeavor of the liberation of the oxadiazoles from **2**−**4** with $Ph_2PCH_2CH_2PPh_2$ (dppe) was not successful from a synthetic viewpoint since the phosphine reduces the Pt(IV) center to Pt(II) without ligand liberation.

We also attempted to perform the liberation starting from the platinum(II) complexes *trans*-[$PtCl_2$(1,2,4-oxadiazole)$_2$] (**5**−**7**) with 2 equiv of dppe (Scheme 2). However, the surprising stability of **5**−**7** toward the substitution for the chelating ligand precluded this route. The replacement of the 1,2,4-oxadiazole species from the platinum(II) complexes with an excess of pyridine was not fully achieved, and the liberated heterocycles were contaminated with unreacted starting Pt(oxadiazole) complexes and with the [$PtCl_2$-(pyridine)$_2$] product, which exhibits a good solubility. Hence, this is not a useful method for that purpose.

## Final Remarks

This work demonstrates that nitriles can be activated, by coordination, toward 1,3-dipolar cycloaddition of dipoles of the propargyl/allenyl anion type[24] and therefore are not

(63) Jørgensen, S. M. *J. Prakt. Chem.* **1886**, *33*, 489.

limited to dipoles of the allyl anion type.[24] The unprecedented resulting [2 + 3] cycloaddition, followed by liberation of the 1,2,4-oxadiazoles formed, which has been achieved for the first time in this work, represents a new and alternative route, performed under mild conditions, to this important class of heterocycles. The only limitation we see so far is the *poor solubility* of the starting materials, making the cycloaddition difficult, and/or the (1,2,4-oxadiazole)platinum-(IV) complexes, which precludes the liberation. However, we anticipate that this general barrier of platinum(IV) chemistry can be overcome with the use of other activating metal centers, and this project is under way in our group. The metal enhancement of the activation of the ligated nitriles is expected to promote other 1,3-dipolar cycloadditions, and the generality of this strategy for the synthesis of heterocycles should be further explored.

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**Supporting Information Available:** Tables of crystallographic data for **2**, **6**, and **8** (PDF). Crystallographic data for **2**, **6**, and **8** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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