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Reactions of Amidoximes with Metal-Activated Nitriles[1]

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Abstract—Metal-mediated reactions of amidoximes with nitrile ligands are discussed and recent works of the author are considered to allow the reader to better understand the amidoxime reactivity patterns. General routes of activation of amidoxime and nitrile substrates in the studied reactions are considered. Reactions employing amidoximes as HO- and HN-nucleophiles, as well as reactions of amidoximes with nitrile ligands leading to heterocyclic systems are discussed.

Keywords: amidoxime, aminonitrone, platinum, transition metal, catalysis

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INTRODUCTION

In accord with IUPAC nomenclature, amidoximes, RC(NH2)=NOH (R = H, Alk, Ar), are derivatives of carboxamides, which differs them from conventional oximes, RC(R')=NOH (R/R' = H, Alk, Ar), which are derivatives of ketones and aldehydes, as a separate class of compounds [1]. While amidoximes and oximes have similar structures, availability of strong +M donor amide group NR2 in amidoximes in many cases causes significantly different reactivity of amidoximes in comparison with conventional oximes. In the case of unsubstituted amide group, amidoximes feature two nucleophilic centers, viz. HO and HN, which additionaly differ reactivity of amidoximes from conventional oximes, in particular, toward nitrile ligands.

Although the versatile chemistry of conventional oximes has been repeatedly reviewed in coordination [2–6] and organic [7, 8] chemistry literature, amidoximes have so far received substantially less attention. Only limited-scope reviews focusing on sorption of heavy metal cationic species by polyamidoxime materials [9–11], and also organic [12, 13] and pharmacological chemistry [13–16] is represented in the literature. In our previous review [17], we comprehensively discussed coordination chemistry and metal-involving reactions of amidoximes. In this review, special attention to the reactions with nitrile ligands will be focused with respect to recent works of the author allowing the deeper understanding of the reaction patterns to be done.

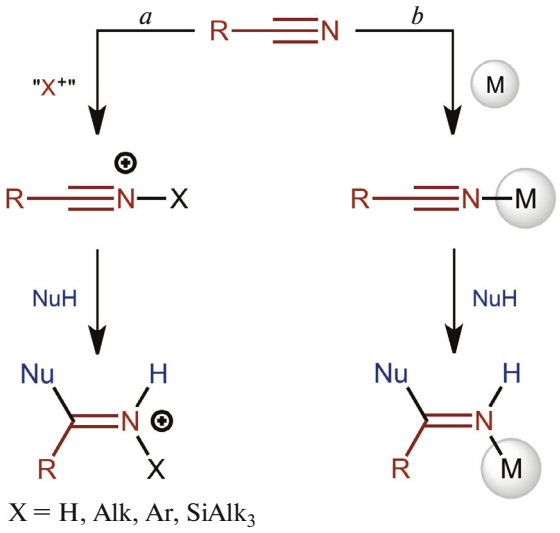
In this review, analysis of general routes of activation of amidoxime and nitrile substrates in the reactions studied is given. Reactions employing amidoximes as HO- and HN-nucleophiles, as well as reactions of amidoximes with nitrile ligands leading to heterocyclic systems, are discussed.

ACTIVATING ROLE OF METAL CENTER IN THE REACTIONS OF AMIDOXIMES WITH NITRILES

Nucleophilic addition to nitriles RCN is an attractive route to preparation of new complex and organic compounds in laboratory and industry [18–24]. Nitriles are hardly reactive substrates toward nucleophilic addition to them. In particular, only nitriles R^1CN featuring strong electron-withdrawing groups R^1 at C≡N triple bond (for example, perfluoroalkyls) are able to react with nucleophiles, especially with amidoximes [25], in mild conditions. Nitriles R^1CN featuring weak electon acceptor or donor groups R^1 do not react with amidoximes under normal conditions and additional electrophilic activation of nitriles and/or nucleophilic activation of amidoximes is required for these reactions proceed. Both types of activation could be achieved by interactions between the substrates with a metal center.

Electrophilic activation of nitriles by metal center. In organic chemistry, electrophilic activation of nitriles is achieved by protonation (Pinner synthesis) [26], alkylation [27], arylation [28], or trialkylsilylation [29] of nitriles at the N atom, but it is necessary to conduct these reactions in dry media and prepared nitrilium salts $[R^1{-}C{\equiv}N{-}R^2]^+$ are unstable under normal conditions due to their extremely high reactivity (Scheme 1*a*).

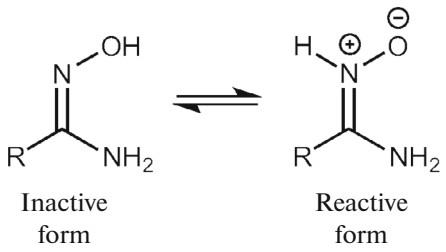
[1] The article was translated by the authors.



Scheme 1.

More convenient route to electrophilic activation of nitriles is coordination to metal center (Scheme 1*b*). These reactions can be conducted in undried solvents and generated nitrile complexes are shelf stable, because of C≡N group in nitrile ligands is activated toward nucleophilic addition in less degree, than in organic nitrilium salts. Our experimental data indicate that the reactivity of nitrile ligands in substrates [R–C≡N–M] toward nucleophilic addition of amidoximes decreases in the following row: $B_{10}H_9$ [30] > Pt(IV) [31] ⩾ Pt(II) [32] ⩾ Zn(II) [33]. Nevertheless, as it is showed below, that even the least activating center of zinc(II) allows the reactions of amidoxime–nitrile ligand coupling can be provided under mild conditions.

Nucleophilic activation of amidoximes by metal center. Stabilization of aminonitrones. Recently it was showed that in the reactions of nucleophilic addition of amidoximes to unsaturated bonds, tautomeric to amidoxime aminonitrones are active species (Scheme 2) [30, 34–36].



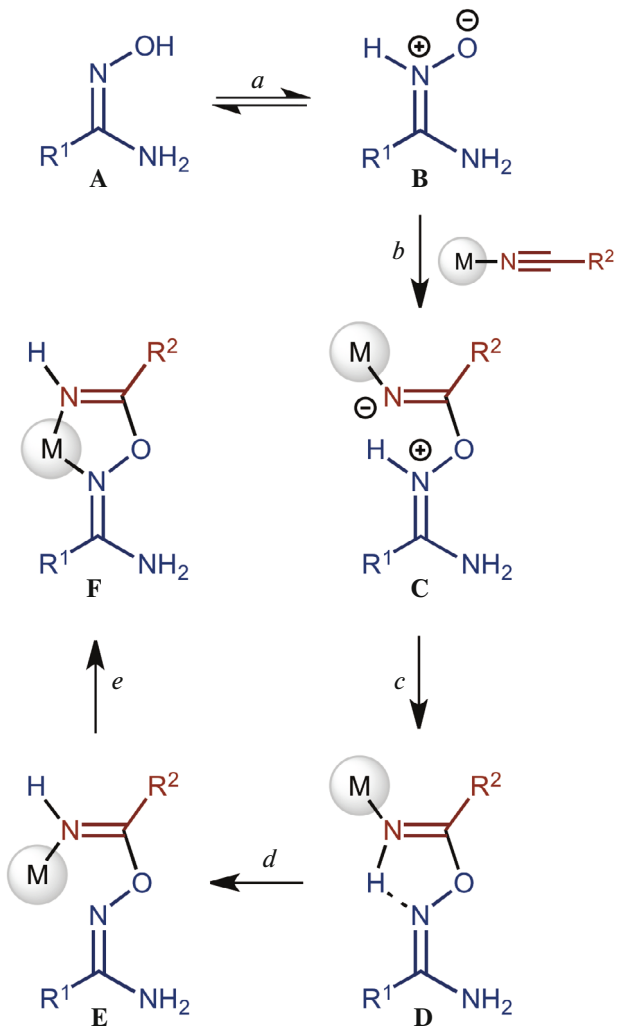
Scheme 2.

Due to this fact, possibility of selective stabilization of amidoxime ligands in the aminonitrone form seems to be an attractive route for metal-mediated catalysis of reactions of nucleophilic addition of amidoximes to unsaturated substrates. General problem of this route is low selectivity of generation of amidoxime complexes. Today at least nine coordination modes of amidoximes to metal center are known and only two of them includes active aminonitrone form of ligated amidoxime. At the same time, prediction of coordination mode of amidoxime to a metal center is complicated [17]. Nevetheless, the author have been succeeded in finding of system realizing nucleophilic activation of amidoxime toward coupling with nitrile ligands via selective stabilization of aminonitrone form of amidoxime by two zinc(II) centers [34].

AMIDOXIMES AS HO-NUCLEOPHILES. GENERATION OF O-IMINOACYL AMIDOXIME COMPLEXES

In this section, two fundamentally different routes of amidoxime–nitrile coupling are discussed, viz. reactions utilizing uncomplexed amidoximes and amidoxime ligands.

Reactions of uncomplexed amidoximes with nitrile ligands. The HO moiety of amidoximes is significantly more reactive toward nucleophilic addition to electrophiles than the NH_2 moiety and consequently generation of *O*-functionalized amidoximes requires no preliminary protection of the NH_2 group. In Scheme 3, schematic representation is given for the reaction of nucleophilic addition of amidoximes by the HO group to nitrile ligands at kinetically inert metal centers, i.e., Pt^{IV}, Pt^{II}, and B^{III} [30–32, 37–39]. At these centers, coordination of amidoxime does not proceed and it plays a role of external nucleophile. At the first step, tautomerization of amidoxime **A** to aminonitrone **B** proceeds (Scheme 3*a*). Next, nucleophilic attack of the O atom of the aminonitrone on the C atom of the C≡N group of the nitrile ligand proceeds giving intermediate **C** (Scheme 3*b*), which further undergoes transformation to product **D** by proton transfer (Scheme 3*c*). The *O*-iminoacyl amidoxime ligand in **D** exists in (*E*)-configuration at the C=N bond and has intramolecular H-bond between the H atom of imine moiety and the N atom of the oxime moiety. In some cases, which are likely caused by steric and electronic factors, configuration of the ligand converses giving products **E** (kinetically inert Pt^{IV} center) or chelated complexes of type **F** (more kinetically labile Pt^{II} center) featuring the (*Z*)-configured ligands.



Scheme 3.

It was shown that amidoximes $R^1C(NHR^2)=NOH$ (R^1 = $PhCH_2$, OC_4H_8N, $R^5C_6H_4$: R^5 = 4-MeO, 2-Me, 4-Me, H, 2-Cl, 4-Cl, 4-Br, 4-CF_3, 4-NO_2; R^2 = H, *n*-Bu, Ph) reacted with 2-nitrilium derivatives of *closo*-decaborate cluster $(Ph_3PR^4)[B_{10}H_9NCR^3]$ (R^3 = Me, Et, *n*-Pr, *iso*-Pr; R^4 = $PhCH_2$, Ph) in MeCN at 20–25°C for 5 min giving products **D** $(Ph_3PR^4)[B_{10}H_9N(H)=C(R^3)ON=C(NHR^2)R^1]$, which were isolated as solids in 57–96% yields [30, 37]. The coupling products underwent slow hydrolysis in undried solvents leading to a mixture of starting amidoximes, 1,2,4-oxadiazoles, 2-ammine *closo*-decaborate and enamines $(Ph_3PR^4)[B_{10}H_9N(H)C(OH)R^3]$ [30, 37].

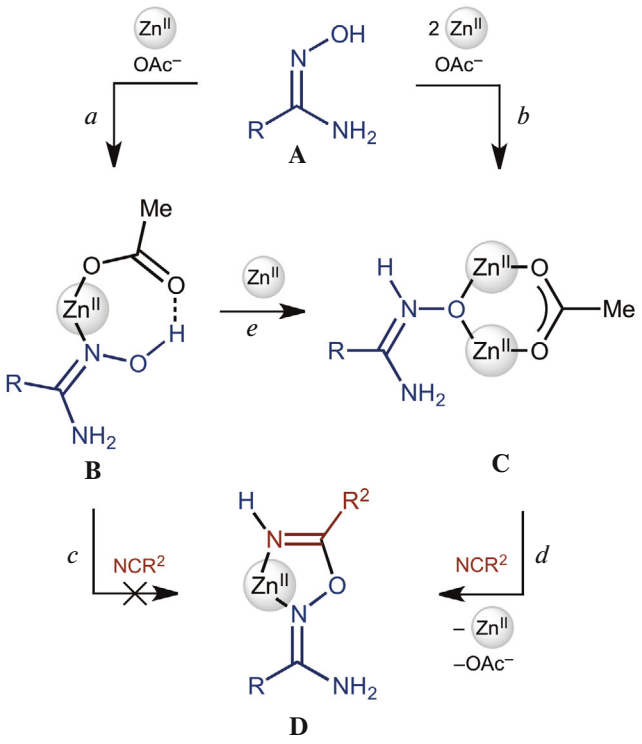
Reactions of nucleophilic addition of amidoximes by the HO group to nitrile ligands at Pt^{IV} center proceeded slower than that with 2-nitrilium *closo*-decaborate clusters. Amidoximes $R^1C(NH_2)=NOH$ (R^1 = Me, $PhCH_2$, Ph) reacted with *trans*-$[PtCl_4(NCR^2)_2]$ complexes in CH_2Cl_2 or $MeNO_2$ at 20–25°C for 15 min giving monoaddition products *trans*-$[PtCl_4(NCR^2)\{H\underline{N}=C(R^2)ON=C(NH_2)R^1\}]$ or bis-additions products *trans*-$[PtCl_4\{H\underline{N}=C(R^2)ON=C(NH_2)R^1\}_2]$ (in 1 : 1 and 2 : 1 molar ratios, respectively). These compounds were isolated in 72–95% yields [31]. The bisaddition products appeared to be stable in undried solvents and in $MeNO_2$ at reflux for 2 h, whereas the monoaddition products underwent complete degradation under the same conditions and decomposed in undried solvents for 3 weeks. It was observed, that depending on the nature of starting nitrile ligand, complexes were generated with ligands in different configurations. Thus, derivatives of conventional nitriles (R^2 = Et, Ph) were formed in (*E*)-configuration, whereas dimethylcyanamide derivatives (R^2 = NMe_2) existed as open-chain species bearing (*Z*)-configured ligands (type E).

Reactions of nucleophilic addition of amidoximes by the HO group to less electrophilic nitrile ligands at the platinum(II) center logically proceeded for longer time. In these reactions, differences in reactivity appeared at qualitative level for both amidoximes and nitriles of different nature. Amidoximes $R^1C(NH_2)=NOH$ (R^1 = Me, OC_4H_8N, 4-$R^3C_6H_4$: R^3 = MeO, Me, H, Cl, CF_3, NO_2) reacted with nitrile complexes *cis*-$[PtCl_2(NCR^2)_2]$ and *trans*-$[PtCl_2(NCR^2)_2]$ (R^2 = Et, *tert*-Bu, Ph, 4-BrC_6H_4, NMe_2) giving mono- and bisaddition products [32, 38, 39]. The reactions with conventional nitrile derivatives (R^2 = Et, *tert*-Bu, Bu, Ph, 4-BrC_6H_4) proceeded leading to open-chain complexes *cis*- or *trans*-$[PtCl_2(NCR^2)_{2-n}\{H\underline{N}=C(R^2)ON=C(NH_2)R^1\}_n]$ (n = 1, 2 with respect to starting molar ratios 1 : 1 or 2 : 1, respectively; type D), whereas dimethylcyanamide derivatives gave chelated complexes *cis*- or *trans*-$[PtCl_{2-n}(NCR^2)_{2-n}\{H\underline{N}=C(R^2)O\underline{N}=C(NH_2)R^1\}_n]Cl_n$ bearing the (*Z*)-configured ligands (n = 1, 2; type F). All reactions proceeded in the solutions of CH_2Cl_2, $CHCl_3$, Me_2CO and $MeNO_2$ (yields 57–92%). In the case of propanenitrile complexes $[PtCl_2(NCEt)_2]$, the reaction of nucleophilic addition of hydroxyguanidine $OC_4H_8NC(NH_2)=NOH$ proceeded for 5 min [39], whereas with conventional amidoximes $R^1C(NH_2)=NOH$ (R^1 = Me, 4-$R^3C_6H_4$: R^3 = MeO, Me, H, Cl, CF_3, NO_2), it required 3–48 h to be completed [32, 38]. For a series of *para*-substituted benzamidoximes, in the reaction with *cis*-$[PtCl_2(NCEt)_2]$ in ace-

tone at 23°C, excellent correlation with σ_{para} constants was observed and reaction parameter was calculated $\rho^{296}(\sigma_{para}) = (-1.81 \pm 0.03)_{p=0.95}$ ($R^2 = 0.9992$). These results indicate significant influence of electronic factors of substituents at the carbamidoxime moiety on reactivity of amidoximes in the reactions of nucleophilic addition of these species by the HO group to nitrile ligands [38]. Changes in the reaction rates were observed also during variation of substituents in nitrile ligands. Dialkylcyanamide complexes appear to be the most reactive toward coupling with amidoximes and aromatic nitrile derivatives were more reactive, than aliphatic nitrile complexes [32].

Reactions of metal-bound amidoximes with nitrile ligands. In the process of reaction of amidoximes with zinc(II) dialkylcyanamide complexes [40] substitution of dialkylcyanamide ligands proceeded leading to amidoxime zinc(II) complexes [33]. The same substitution was observed also for less reactive aromatic and aliphatic nitrile ligands. Thereby, amidoxime–nitrile coupling at the zinc(II) center is fundamentally different from the reactions at such kinetically inert centers, as boron(III), platinum(II), and platinum(II), because of this coupling proceeds between metal-bound organic substrates.

Coupling of metal-bound amidoximes and nitrile ligands is represented in Scheme 4 [33, 34]. It was found, that in dependence of molar ratio between zinc(II) species, acetate ions, and amidoximes, it is possible to prepare complexes bearing amidoxime ligands in different coordination modes. Then $Zn(OAc)_2 \cdot 2H_2O$ reacts with 2 equivs. of amidoxime $R^1C(NH_2)$=NOH (**A**), where R^1 = Et, *tert*-Bu, Ph, 2-ClC_6H_4, in acetone at 50°C for 5 min complexes $[Zn(OAc)_2\{R^1C(NH_2)=\underline{N}OH\}_2]$ (**B**) are generated (isolated yields 75–82%; Scheme 4*a*) [34]. In these complexes, amidoxime is coordinated to the zinc(II) center by the oxime N atom and intramolecular H-bond exists between the H atom of HO group and the O atom of the acetate ligand. In the case of molar ratio of the reagents 3 : 2 : 4 (Zn^{II} : OAc^- : amidoxime), trimetallic zinc(II) complexes $[Zn_3(\mu_2\text{-}OAc)_2\{\mu_2\text{-}R^1C(NH_2)=N(H)\underline{O}\}_4(H_2O)_6]^{4+}$ (**C**) featuring two bridging acetate ligands and four bridging aminonitrone ligands are formed (Scheme 4*b*).



Scheme 4.

Complexes **B** and **C** demonstrated different reactivity toward dimethylcyanamide $NCNMe_2$ [34]. Complexes **C** bearing bridging aminonitrone ligands reacted with dimethylcyanamide in EtOAc for 3 h at 20–25°C giving coupling products $[Zn(OTf)_2\{H\underline{N}=C(NMe_2)O\underline{N}=C(NH_2)R^1\}_2]$ (**D**), which were isolated in 76–82% yields (Scheme 4*d*), whereas amidoxime complexes **B** did not react with $NCNMe_2$ at 20–25°C at least for 24 h (Scheme 4*c*) and gave a mixture of unidentified products at 50°C for 3 h. Nevertheless, after addition of 1 equiv. of zinc(II) to complexes **B** they formed complexes **C**, which further reacted with dimethylcyanamide. Thus, it was shown, that for successful reaction of nucleophilic attack of the O atom of amidoxime ligands to nitrile substrates, the amidoxime ligands should be stabilized by a metal in the corresponding aminonitrone form [34].

Another example of the nucleophilic addition reaction of the HO group of amidoxime ligands to nitriles at the zinc(II) center is reaction of $ZnCl_2$ with 1 equiv. of $R^1C(NH_2)$=NOH (R^1 = Me, Ph) and excess of nitrile R^2CN (R^2 = Et, Ph, N(H)COPh, NMe_2, OC_4H_8N) in EtOAc at 80°C for 20–48 h [33, 41]. This reaction resulted in formation of chelated zinc(II) complexes $[ZnCl_2\{H\underline{N}=C(R^2)O\underline{N}=C(NH_2)R^1\}]$ (75–96% isolated yields). After addition of a solution of amidoxime in EtOAc to a solution of $ZnCl_2$ in EtOAc, immediate formation of colorless precipitate of a mix-

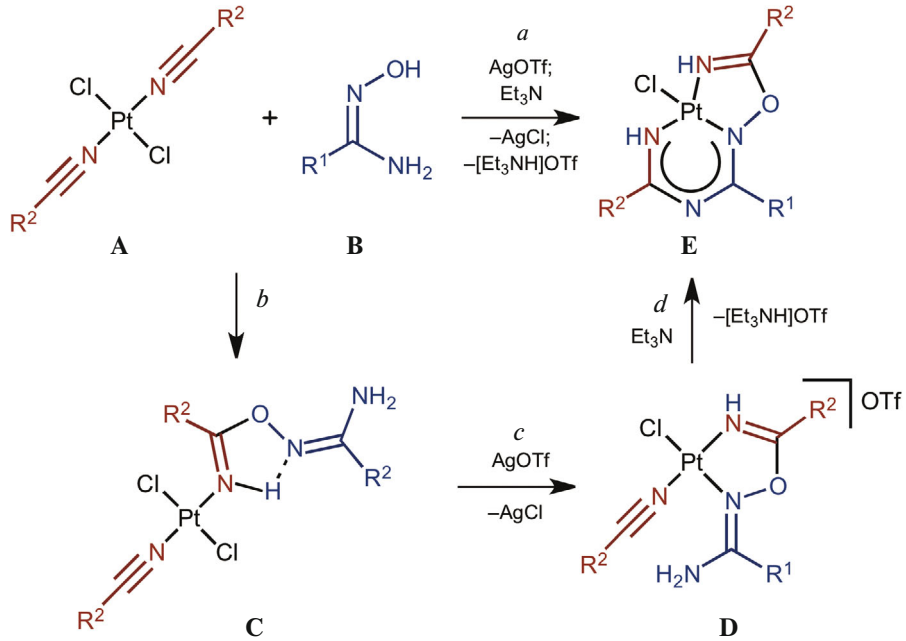
ture of amidoxime zinc(II) complexes having $[ZnCl_2\{R^1C(NH_2)=NOH\}]$ gross composition was observed. Further reaction proceeded under the heterogeneous conditions at vigorous stirring. Due to the employment of EtOAc as a solvent in this reaction, one can conclude generation of active aminonitrone complexes **C**, as a result of zinc(II)-mediated hydrolysis of the solvent to EtOH and AcOH [34], but in these work no attempts to identify these intermediates were undertaken [33, 41].

In all reactions of nucleophilic addition of amidoximes to nitriles by the HO group, a trend to increase of reactivity of the oxime substrates during increase of electron-donor properties of substituents in them is observed. Thus, hydroxyguanidine $R_2NC(NH_2)=NOH$ is more reactive than aliphatic amidoximes $AlkC(NH_2)=NOH$, which, in turn, are more reactive, than aromatic amidoximes $ArC(NH_2)=NOH$ [30]. All studied amidoximes are significantly more reactive toward nucleophilic addition to nitrile ligands, than ketoximes [30, 32, 38]: the amide moiety has so strong $+M$ effect, as even the least reactive amidoxime $4\text{-}O_2NC_6H_4C(NH_2)=NOH$ reacts with nitrile ligands faster than ketoximes [38].

AMIDOXIMES AS HN-NUCLEOPHILES. GENERATION OF 1,3,5-TRIAZAPENTADIENATE COMPLEXES

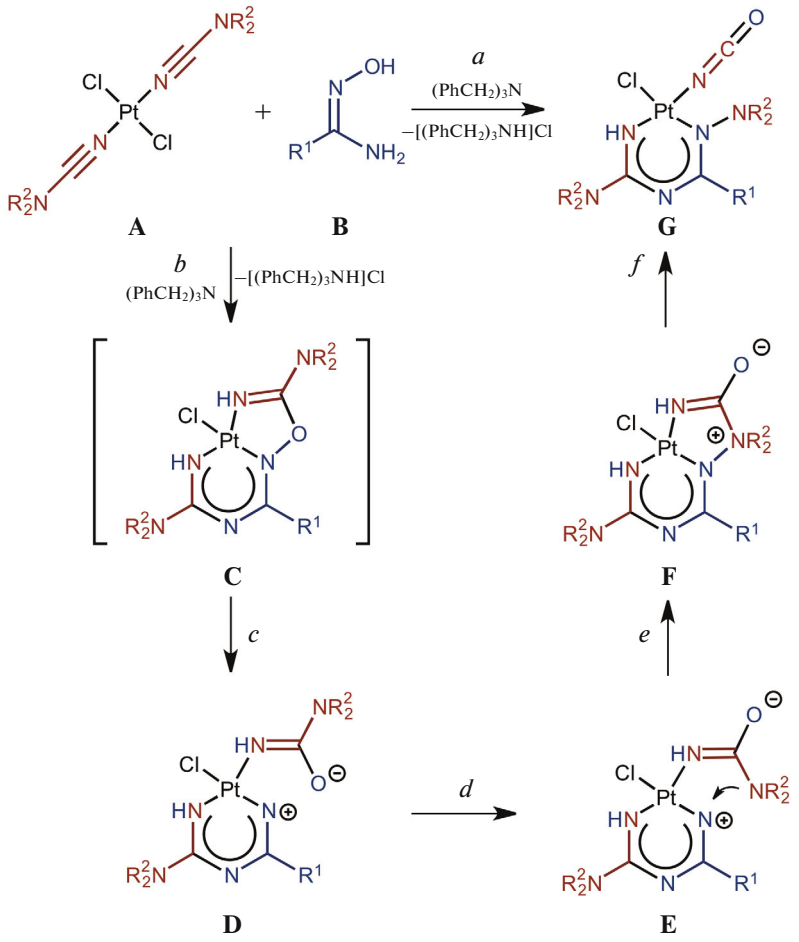
Nucleophilc properties of the amide N atom of amidoximes are lower than that of the oxime O atom. Owing this reason, selective nuclephilic addition of amidoximes to nitrile ligands by the amide group is known only for *O*-substituted amidoximes played a role of *N*-functionalized amidines [42, 43].

Generation of 1,3,5-triazapentadienate platinum(II) complexes is represented in Scheme 5 [44]. It was observed, that aromatic amidoximes $R^1C(NH_2)=NOH$ (**B**), where R^1 = 4-MeC_6H_4, Ph, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-$O_2NC_6H_4$, reacted with complexes *trans*-$[PtCl_2(NCR^2)_2]$ (**A**), where R^2 = Ph, 2-ClC_6H_4, 4-$CF_3C_6H_4$, bearing aromatic nitrile ligands in the presence of 1 equiv. of AgOTf in the basic media (5-fold excess of Et_3N) for 4–5 h giving the products obtained by the nucleophilc attack of the NH_2 group to the C≡N bond—1,3,5-triazapentadientate complexes **E** (Scheme 5*a*) [44]. Pausible mechanism of the reaction includes nucleophilic attack of amidoxime by the HO group to the first equiv. of nitrile ligands (Scheme 5*b*) leading to intermediate **C**. Then, chelate ring closure proceeds due to Ag^+-mediated decoordination of the chloride ligand (Scheme 5*c*) giving intermediate **D**. At the last step, nucleophilic attack of the amidate NH^- group (generated in the basic media by deprotonation of the NH_2 group) to the second equiv. of the nitrile ligands proceeds (Scheme 5*d*) giving the final product **E**. Intermediates **C** and **D** were identified and their consequent transformations were studied in the reaction mixture. In addition, it was shown by theoretical calculations that at the step *d*, the attack proceeds by the NH^- group, whereas for the attack by the NH_2 group, no transition state were found [44].



Scheme 5.

In the case of utilization of dialkylcyanamide platinum(II) complexes *trans*-$[PtCl_2(NCNR^2_2)_2]$ in this reaction instead of the aromatic nitrile complexes *trans*-$[PtCl_2(NCAr)_2]$, the reaction did not stop at the product **E** (Scheme 5) and proceeds further leading to formation of amidrazone platinum(II) complexes (Scheme 6) [45]. Amidoximes $R^1C(NH_2)$=NOH (**B**), where R^1 = 4-MeC_6H_4, Ph, 4-NCC_6H_4, 4-$O_2NC_6H_4$, reacted with dialkylcyanamide complexes *trans*-$[PtCl_2(NCNR^2_2)_2]$ (**A**), where R^2_2 = Me_2, C_5H_{10}, in the presence of $(PhCH_2)_3N$, playing a role of the NH-nucleophiles, giving cyanate amidrazone complexes **G** (Scheme 6) [45].



Scheme 6.

Plausible mechanism of the reaction includes initial generation of intermediate **C** by consequent set of nucleophilic attacks of amidoxime by the HO and HN groups to dialkylcyanamide ligands (Scheme 6*b*). Intermediate **C** then undergoes spontaneous heterolytic splitting of the N–O bond (Scheme 6*c*), inversion of the C=N bond configuration (Scheme 6*d*), and intramolecular electrophilic substitution at the N atom of the NR^2_2 group (Scheme 6*e* and 6*f*) giving final product **G**. Intermediate **C** was not unambiguously identified in the reaction mixture due to its unstability, but its congener – platinum(IV) complex $[PtCl_3\{H\underline{N}=C(NMe_2)O\underline{N}=C(Ph)NC(NMe_2)=\underline{N}H\}]$ was isolated from the reaction mixture and characterized by single-crystal XRD [31].

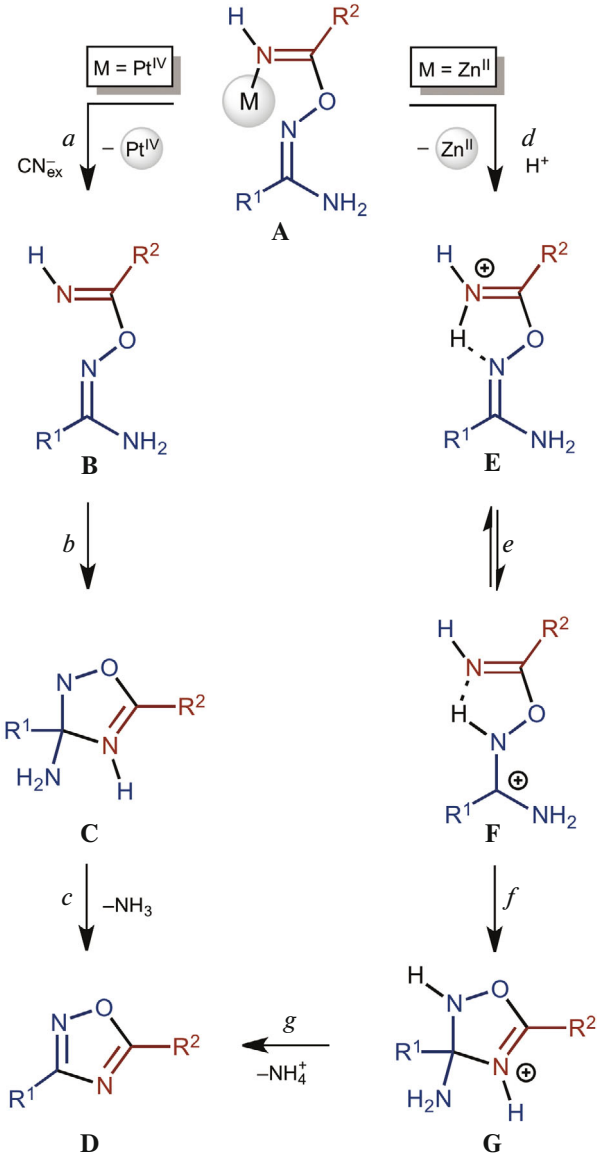
METAL-MEDIATED REACTIONS OF HETEROCYCLIZATION OF AMIDOXIMES

Reactions of amidoximes with nitrile ligands allow the preparation of not only the products of *O*- and *N*-functionalization, but also to such five-membered heterocycles, as 1,2,4-oxadiazoles and 1,2,4-triazoles. These five-membered heterocycles are generated via intramolecular reactions of heterocyclization of the coupling products. In this section, firstly, reactions of generation of 1,2,4-oxadiazoles will be discussed, and after that reaction leading to 1,2,4-triazoles will be considered.

Products of the coupling of amidoximes with bisnitrile platinum(IV) complexes *trans*-$[PtCl_4\{H\underline{N}=C(R^2)ON=C(NH_2)R^1\}_2]$ (R^1 = Me, $PhCH_2$, Ph; R^2 =

Me_2N, Et, Ph) are stable compounds toward acids and bases, but underwent fast (less than for 1 min) decomposition in the presence of excess of NaCN in $(CD_3)_2SO$ solution (Scheme 7*a*) giving *O*-iminoacyl amidoximes, $Na_2[Pt(CN)_6]$, and NaCl (quantitative yields; Scheme 7) [31]. Uncomplexed imines **B** appeared to be unstable in the solution of $(CD_3)_2SO$ at 20–25°C and underwent transformations by two routes, viz. heterocyclization to 1,2,4-oxadiazoles **D** (12–32%; Scheme 7*b*, 7*c*) and splitting to starting nitrile and amidoxime (R^2 = Et, Ph; 68–88%) with half-life ca. 5–8 days. Dialkylcyanamide derivatives **B** ($R^2 = Me_2N$) were significantly less stable and underwent a series of highly unselective transformations with half-life ca. 7 min. Oxadiazoles **D** were detected by ^{1}H NMR spectroscopy only in trace amounts and the general products were dimethylurea $Me_2NC(=O)NH_2$ and *N*-substituted ureas $R^2NHC(=O)NH_2$ (30–35%) generated via Tiemann rearrangement [31]. The most probably, this unselective decomposition is caused by high basicity of the N atom of uncomplexed dialkylcyanamide derivatives bearing isourea moiety providing basic media with consequent set of unselective transformations. At the same time, propanenitrile and benzonitrile derivatives feature the less basic N atom in the structures and underwent more selective transformations in more neutral media. It was found, that the yield of 1,2,4-oxadiazole **D** increases in the case of electron-withdrawing substituents in the amidoxime part and electron-donor substituents in the nitrile part of the *O*-iminoacyl amidoximes **B**. These observations indicate that the heterocyclization proceeded via nucleophilic attack of the imino group to the carbamidoxime C atom (Scheme 7*b*) with consequent elimination of NH_3 molecule (Scheme 7*c*) [31].

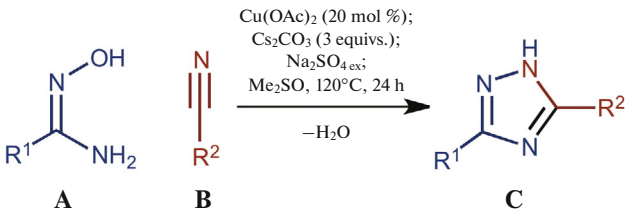
When 4-$MeC_6H_4SO_3H$ reacted with iminoacyl amidoxime zinc(II) complexes $[ZnCl_2\{HN{=}C(R^2)ON{=}C(NH_2)R^1\}]$ (R^1 = Me, Ph; $R^2 = Me_2N$, OC_4H_8N, PhCONH, Et, Ph) in methanol for 5 min, iminium salts **E** were generated (79–99% isolated yields; Scheme 7*d*) [33, 41]. Salts **E**, similarly to uncomplexed imines **B**, were unstable toward heterocyclization to 1,2,4-oxadiazles **D**, but their reactivity appear to be opposite. The cyanamide derivatives **E** ($R^2 = Me_2N$, OC_4H_8N, PhCONH) were stable at 20–25°C and they were not only isolated from the reaction mixture, but also characterized by single-crystal XRD. They transform to the 1,2,4-oxadiazoles only at 65°C for 48 h ($R^2 = Me_2N$, OC_4H_8N) or 1 h (R^2 = PhCONH) giving the products in 37–100% after purification. Propanenitrile and benzonitrile derivatives (**E**; R^2 = Et and Ph, respectively) were unstable in solutions even at 20–25°C. They transformed to 1,2,4-oxadiazoles **D** (78–93%) at 65°C for 5–15 min. Different reactivity of iminium salts **E** again can be explained in terms of basicity of the N atom of imino group and this was confirmed by theoretical calcualtions [41]. On the one hand, in the case of dialkylcyanamide derivatives, basicity of the N atom in the nitrile part of molecule is significantly higher, than that of the oxime N atom and, consequently, prototropic equilibrium (Scheme 7*e*) was dominantly shifted to **E**. On the other hand, basicity of the N atom in nitrile part of molecule of propanenitrile and benzonitrile derivatives is similar to that of the oxime N atom providing higher equilibrium concentration of **F** [41]. Intermediate **F** has nucleophilic imino group and electrophilically activated carbamidoxime C atom, which provides ring closure giving intermediate **G** (Scheme 7*f*). Intermediate **G** transforms to 1,2,4-oxadiazole **D** via elimination of NH_4^+.



Scheme 7.

H. Xu with coworkers found, that amidoximes $R^1C(NH_2){=}NOH$ (**A**; R^1 = *n*-Pr, cyclo-Pr, *tert*-Bu, cyclopentyl, *n*-undecyl, 3-pyridyl, 4-$O_2NC_6H_4$, 4-ClC_6H_4, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$) reacted with

nitriles R^2CN (**B**; R^2 = 3-pyridyl, 4-$O_2NC_6H_4$, 4-ClC_6H_4, Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$) in the presence of $Cu(OAc)_2$ (20 mol %) and excess of Cs_2CO_3 and Na_2SO_4 in dry Me_2SO at 120°C for 24 h giving 1,2,4-triazoles **C**, which were isolated in 41–83% yields (Scheme 8) [46].



Scheme 8.

A mechanism suggested by the authors [46] was not confirmed experimentally and requires refinement. The author of this review, in turn, suggests that plausible mechansim could include generation of intermediate square-planar copper(II) complex similar to **C** in Scheme 6 and consequent retrocoupling at the O–C bond, followed by heterolytic splitting of the N–O bond and formation of the N–N bond.

In conclusion it should be noticed that availability of the NH_2 group in amidoximes provides significant differencies in their reactivity from that of conventional oximes toward nitrile ligands. This is shown by two aspects: (*i*) the strong +*M* effect of the NH_2 group causes significantly higher reactivity of the oxime HO group toward nucleophilic addition to nitrile ligands; (*ii*) in spite of the NH_2 moiety has low reactivity in neutral media, it can be deprotonated even in the slightly basic media giving NH^- moiety, which is able to nucleophilically attack a coordinated nitrile.

These differencies in reactivity of amidoximes allow providing such reactions, which cannot be realized for conventional oximes. In particular, 1,2,4-oxadiazoles can be generated via reaction of amidoxime–nitrile coupling with consequent heterocyclization of the coupling products. Moreover, it is possible to prepare 1,3,5-triazapentadiene systems featuring amidoxime or amidrazone moieties, which can transform to 1,2,4-triazoles at the platinum(II) center.

The author expresses the hope that this review will stimulate readers to develop little-known metal-mediated chemistry of amidoximes, not only with respect to nitrile ligands, but also to other unsaturated metal-activated small molecules.

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