



An efficient Pd-catalyzed hydration of nitrile with acetaldoxime

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ABSTRACT

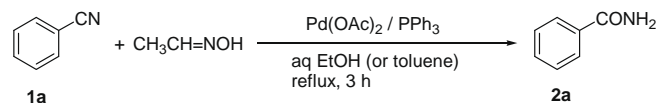
An efficient palladium-catalyzed protocol for the hydration of nitrile to amide with acetaldoxime has been developed. A plausible mechanism was suggested involving the first Pd(II)-catalyzed nitrile–oxime coupling and the following disruption of the intermediate into amide and acetonitrile in a concerted manner.

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The hydration of nitriles to the corresponding amides is very important in view of its broad industrial and pharmacological applications.^{1–3} Hydrolysis of amides to carboxylic acids is a serious problem in many cases under the conventional hydration conditions.² Some useful methods for the selective hydration of nitriles to amides have been developed including the use of TFA/H₂SO₄^{2a} and the use of H₂O₂/K₂CO₃/DMSO at low temperature.^{2b} Recently, transition metal-catalyzed selective hydration of nitriles has also been reported involving the use of Rh,^{3a,b} Pt,^{3c,d} Ru,^{3e–h,m} Ir,³ⁱ Mo,^{3j} and Co.^{3k,l}

To the best of our knowledge, an efficient Pd-catalyzed hydration of nitriles to amides has not been reported.⁴ Maffioli et al. reported the Pd-catalyzed reversible transfer of water between amide and nitrile.^{5a} Very recently, we observed that dehydration of aldoximes to nitriles can be catalyzed by palladium, and that the liberated water can be transferred to CH₃CN to form acetamide.⁶ The Pd-catalyzed dehydration of aldoxime was effective either in toluene or in acetonitrile, thus we proposed two types of plausible mechanisms: one involved the first oxidative addition of N–O bond to Pd(0) followed by β-syn elimination process and the other is a Pd(II)-catalyzed concerted mechanism involving the transfer of water from aldoxime to acetonitrile.⁶ Based on our previous results, we expected that we could develop an efficient Pd-catalyzed hydration method of nitriles to amides. As shown in Scheme 1, we chose acetaldoxime as an efficient water surrogate which could deliver the water molecule to nitrile.

In order to examine the feasibility of our rationale and find optimum conditions, we carried out the reaction of benzonitrile (**1a**) under various conditions and the results are summarized in Table 1. The reaction of **1a** in the presence of Pd(OAc)₂/PPh₃ and acetaldoxime (2 equiv) in dry toluene⁶ produced benzamide (**2a**) in 87% at 80 °C for 3 h as given in entry 1. The reaction in aqueous EtOH (reflux, 3 h) gave similar yield (89%, entry 2).⁷ The reaction at 40 °C required longer reaction time (15 h) and gave diminished yield (entry 3). The use of excess amounts of acetaldoxime (5.0 equiv) did not improve the yield of benzamide (entry 4). With 0.5 equiv of acetaldoxime the reaction was not complete even after long time (12 h). The reaction without acetaldoxime did not produce benzamide at all even in the presence of Pd(OAc)₂/PPh₃ (entry 5). However, the reaction of **1a** and acetaldoxime produced benzamide although the yield was low (43%) even in the absence of Pd(OAc)₂ (entry 6), presumably by the formation of nitrile–oxime adduct (*O*-imidoyl oxime) via the nucleophilic attack of acetaldoxime to free benzonitrile (vide infra).^{1d} When we reduced the amounts of Pd(OAc)₂ to 5 mol % (entry 7), 5 h was required and the yield was slightly reduced (73%). The yield was also reduced slightly without PPh₃ (entry 8). In addition, we examined the reaction of **1a** in the presence of acetamide instead of in the presence of acetaldoxime (entries 9 and 10).^{5a} The



Scheme 1.

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Table 1
Optimization of reaction conditions for the hydration of **1a** to **2a**

Entry	Conditions ^a	2a (%)
1	Pd(OAc) ₂ (10 mol %), PPh ₃ (20 mol %), CH ₃ CH=NOH (2.0 equiv), toluene, 80 °C, 3 h	87
2	Pd(OAc) ₂ (10 mol %), PPh ₃ (20 mol %), CH ₃ CH=NOH (2.0 equiv), H ₂ O/EtOH, reflux, 3 h	89
3	Pd(OAc) ₂ (10 mol %), PPh ₃ (20 mol %), CH ₃ CH=NOH (2.0 equiv), H ₂ O/EtOH, 40 °C, 15 h	68
4	Pd(OAc) ₂ (10 mol %), PPh ₃ (20 mol %), CH ₃ CH=NOH (5.0 equiv), H ₂ O/EtOH, reflux, 3 h	86
5	Pd(OAc) ₂ (10 mol %), PPh ₃ (20 mol %), no CH ₃ CH=NOH, H ₂ O/EtOH, reflux, 48 h	0 ^b
6	No Pd catalyst, PPh ₃ (20 mol %), CH ₃ CH=NOH (2.0 equiv), H ₂ O/EtOH, reflux, 48 h	43 ^b
7	Pd(OAc) ₂ (5 mol %), PPh ₃ (10 mol %), CH ₃ CH=NOH (2.0 equiv), H ₂ O/EtOH, reflux, 5 h	73
8	Pd(OAc) ₂ (10 mol %), no PPh ₃ , CH ₃ CH=NOH (2.0 equiv), H ₂ O/EtOH, reflux, 3 h	82
9	Pd(OAc) ₂ (10 mol %), PPh ₃ (20 mol %), CH ₃ CONH ₂ (4.0 equiv), H ₂ O/EtOH, reflux, 36 h	53 ^b
10	Pd(OAc) ₂ (10 mol %), PPh ₃ (20 mol %), CH ₃ CONH ₂ (4.0 equiv), H ₂ O/EtOH, reflux, 36 h	10 ^b

^a The ratio of H₂O/EtOH is 1:4 (entries 2–10), but the ratio is not critical. The reaction in water or in EtOH showed almost same reactivity.

^b Small amounts of benzoic acid were observed.

reaction of **1a** in the presence of acetamide (4.0 equiv) in aqueous EtOH at room temperature gave low yield of product (53%) and required long time (36 h) in our hand contrary to that described in the reported paper.^{5a} The reaction at refluxing temperature showed the formation of many intractable side products and we could not isolate benzamide in appreciable yield (entry 10).

Based on the experimental results, we can show definitively that acetaldoxime could be used as an efficient water surrogate in the Pd-catalyzed hydration of benzonitrile. Thus, we examined the generality of the reaction with various nitriles under the optimized conditions (entry 2 given in Table 1), and the results are summarized in Table 2.⁸ The reactions of EWG-substituted aromatic nitriles (entries 2 and 3) as well as of EDG-substituted nitriles (entries 4 and 5) showed good results. The reaction of α -phenylcinnamitrile (**1f**) was not complete after 12 h even in the presence of 4.0 equiv of acetaldoxime, and **1f** was recovered in 21% (entry 6). The reactions of acrylonitrile (entry 7) and aliphatic nitriles (entries 8 and 9) also produced the corresponding amides in good yields. The reaction of benzoylacetoneitrile (**1j**) showed the formation of some intractable side products and the yield was moderate (77%). The reaction of **1j** in toluene (conditions given in entry 1, Table 1) did not improve the yield.

The reaction mechanism could be postulated tentatively as in Scheme 2 involving the first Pd(II)-catalyzed nitrile–oxime coupling^{1c,d,9} to form the intermediate (**I**) and the following disruption of (**I**) into benzamide and acetonitrile in a concerted manner.^{1d} Coordination of a nitrile to an electron-withdrawing transition metal ion results in an enhanced electrophilicity of the nitrile carbon, thus making it susceptible to nucleophilic attack.^{1c,d,3e–g,k,4b} The metal-mediated nitrile–oxime coupling reactions can be catalyzed by oxovanadium(IV), platinum(IV), rhenium(IV), rhodium(III), and Ni(II).^{1c} Although Pd(II)-mediated nitrile–oxime coupling has not been reported, similar additions of various nucleophiles to Pd(II)-activated organonitriles have been documented.^{9,4b} The mechanism has to be studied more,¹⁰ but we found an efficient protocol for the Pd-catalyzed hydration of nitriles to amides mediated by acetaldoxime.

The use of acetonitrile as a solvent is not appropriate. Actually, the reaction of **1a** and acetaldoxime (2.0 equiv) in acetonitrile produced acetamide (71%) as the major product together with low yield of **2a** (13%) and most of **1a** was recovered (79%). Thus toluene,

Table 2
Pd-catalyzed hydration of nitriles to amides^a

Entry	Nitrile	Amide (%)
1		2a (89)
2		2b (87)
3		2c (90)
4		2d (94)
5		2e (93)
6		2f (76) ^b
7		2g (91)
8		2h (86)
9		2i (88)
10		2j (77) ^c

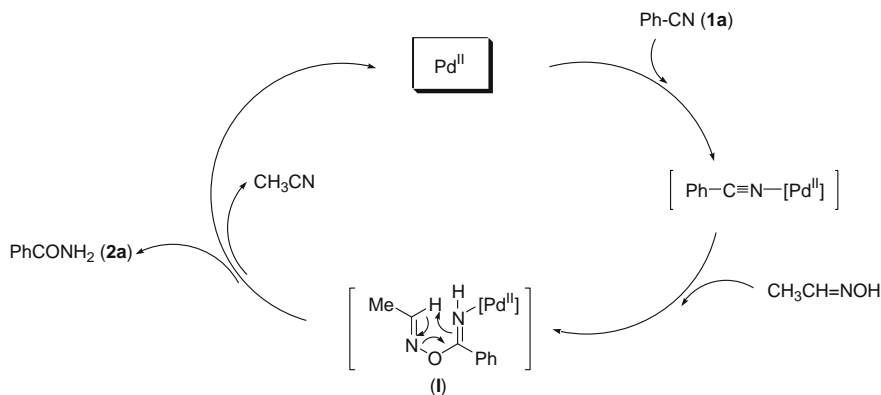
^a Conditions: Nitrile (2.0 mmol), CH₃CH=NOH (4.0 mmol), Pd(OAc)₂, (10 mol %), PPh₃ (20 mol %), H₂O/EtOH (1:4), reflux, 3 h.

^b Reaction time was 12 h and not completed (**1f** was recovered in 21%).

^c Intractable side products were formed.

water, ethanol, and aqueous ethanol can be used as the reaction media although we used aqueous ethanol throughout the whole entries.⁷ The use of ketoxime such as cyclohexanone oxime instead of acetaldoxime was ineffective. Acetaldoxime is the reagent of choice based on the following merits: (i) the most effective water surrogate, (ii) commercial availability in low price, and (iii) easy separation of product from the side products, acetonitrile, and acetamide.

In summary, an efficient palladium-catalyzed protocol for the hydration of nitrile to amide with acetaldoxime has been disclosed. A tentative but plausible mechanism was suggested involving the first Pd(II)-catalyzed nitrile–oxime coupling and the following disruption of the intermediate into benzamide and acetonitrile in a concerted manner.



Scheme 2.

Acknowledgments

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- Kim, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1717–1719, and further references cited therein. During the previous Pd-catalyzed dehydration reaction of 4-nitrobenzaloxime in CD₃CN in NMR tube, we observed the formation of CD₃CONH₂ (unpublished results).
- In the reaction, acetamide was isolated in 42% and the results stated that acetaldoxime was converted into acetonitrile and acetamide. Actually, when the reaction of acrylonitrile (**1g**) was carried out in D₂O in NMR tube we observed the formation of acrylamide (**2g**), acetonitrile, and acetamide, and acetaldoxime disappeared completely.
- Typical procedure for the synthesis of benzamide:** A mixture of benzonitrile (**1a**, 206 mg, 2.0 mmol), acetaldoxime (236 mg, 4.0 mmol), Pd(OAc)₂ (45 mg, 10 mol %), and PPh₃ (105 mg, 20 mol %) in aqueous EtOH (H₂O/EtOH, 1:4, 3 mL) was heated to reflux for 3 h under nitrogen atmosphere. The reaction mixture was filtered through a Celite pad and washed with EtOH/CH₂Cl₂. After removal of solvent and column chromatographic purification process (hexanes/EtOAc/CHCl₃, 1:1:1) benzamide (**2a**) was obtained as a white solid, 216 mg (89%). The synthesized compounds were identified by comparing the melting points with the reported ones and we characterized the structure by their ¹H NMR and/or IR in some cases.
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- Hydration of **1a** with 3 mol % Pd(PPh₃)₄ in the presence of acetaldoxime (2.0 equiv) in aqueous EtOH (reflux, 3 h) also produced **2a** in a similar yield (87%). The results stated that nitrile-oxime adduct could also be generated by the nucleophilic attack of acetaldoxime to activated benzonitrile by coordination-unsaturated low-valent Pd species.