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Synthesis of Nitriles via Palladium-Catalyzed Water Shuffling from Amides to Acetonitrile

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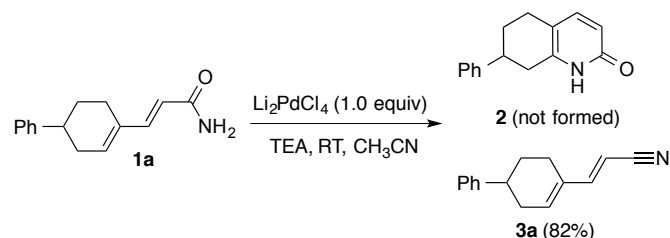
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Palladium-catalyzed synthesis of nitriles from amides has been described. Two similar, but complementary reaction conditions have been identified to convert various amides including $\alpha,\beta,\gamma,\delta$ -unsaturated amides, cinnamides, aromatic amides and alkyl amides to the corresponding nitriles in good to excellent yield.

Nitriles are widely used as starting materials in material, pharmaceutical, agrochemical, and fine chemical industries.¹ The nitrile group is an important functional group involved in various synthetic transformations in making complex and functional molecules. Therefore, many methods have been developed to produce nitriles.² Among the various known methods, synthesis of nitriles from dehydration of amides has been commonly used.³ However, most of the conventional dehydration methods involve using more than stoichiometric amounts of highly reactive reagents such as thionyl chloride, phosphorus pentoxide and phosphorus oxychloride, which renders these protocols incompatible with substrates containing sensitive functional groups.⁴ While mild reagents have been employed later, most of them require special handling and storage.⁵ Recently, significant progresses have been made in catalytic dehydration of amides to nitriles using transition metal catalysts⁶ and non-metal based catalysts.⁷

Our recent interest in 2-pyridone-containing biologically active natural products such as lyconadin A⁸ prompted us to develop new protocols to synthesize 2-pyridones in complex settings. Inspired by the synthesis of 2-pyridones from $\alpha,\beta,\gamma,\delta$ -unsaturated amides using stoichiometric amount of Li_2PdCl_4 in CH_3CN reported by Kasahara and Saito back in 1975,⁹ we wondered the possibility of converting $\alpha,\beta,\gamma,\delta$ -unsaturated amide such as **1a** to the corresponding 2-pyridone **2** (Scheme 1). When **1a** was subjected to the Kasahara-Saito condition, however, desired 2-pyridone **2** was not observed, instead unsaturated nitrile **3a** was produced in 82% yield. The structure of **3a** was unambiguously confirmed by X-ray crystallography.¹⁰ So far, there is only one report about palladium-

catalyzed dehydration of aromatic and aliphatic amides, but no unsaturated amides were explored in the report.^{6b} Generally, dehydration of unsaturated amides such as **1a** to unsaturated nitriles has been underexplored though the latter have shown broad synthetic applications.¹¹ Herein, we report a new palladium-catalyzed dehydration of various amides including $\alpha,\beta,\gamma,\delta$ -unsaturated amides, cinnamides, aliphatic amides, and aromatic amides to the corresponding nitriles.



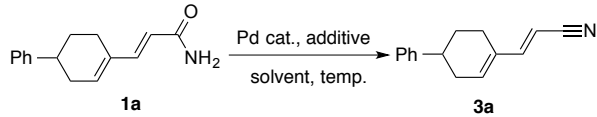
Scheme 1. Our preliminary study.

Results and Discussion

Using compound **1a** as model substrate, we first started to identify a condition employing catalytic amount of palladium catalyst. As summarized in table 1, dehydration product was obtained in 27% yield with PdCl_2 (0.1 equiv) in the presence of LiCl (2.0 equiv), AgOAc (3.0 equiv), and triethylamine (TEA, 3.0 equiv) in CH_3CN (entry 1). When TEA was removed from the reaction system, the yield for the formation of **3a** dramatically increased to 96% (entry 2). While removal of LiCl slightly reduced the reaction yield (entry 3), removal of AgOAc was deleterious and the reaction yield dropped to 8% (entry 4). AgOAc was commonly used as an oxidant to regenerate Pd(II) from Pd(0) . But in our case it could be replaced with NaOAc while the reaction yield remained decent (74%, entry 5). Similar result was obtained with Cu(OAc)_2 (entry 6). These results indicate that the main role of AgOAc or Cu(OAc)_2 is a

source of acetate counter anion. No product was formed without PdCl₂ (entry 7-9). When CH₃CN was replaced with Toluene or DMF, the reaction yield dropped to 8% or 15% respectively. We tried to lower the loading of PdCl₂ and AgOAc as well, but reduced product yield accompanied (entry 12-15).

Table 1. Reaction condition optimization.



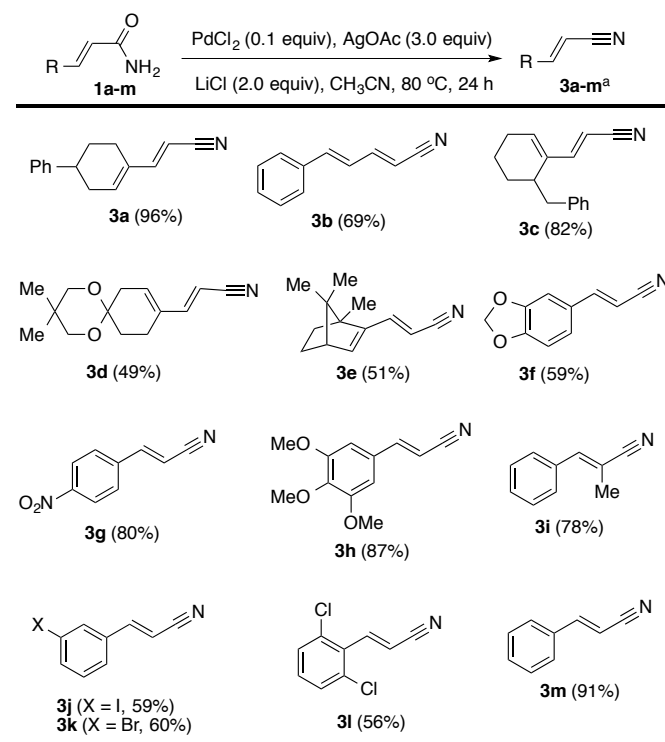
Entry	Reaction Condition ^a	Yield ^b
1	PdCl ₂ , LiCl, AgOAc, TEA (2.0 equiv), CH ₃ CN	27%
2	PdCl₂, LiCl, AgOAc, CH₃CN	96%
3	PdCl ₂ , AgOAc, CH ₃ CN	91%
4	PdCl ₂ , CH ₃ CN, 80-110 °C	8%
5	PdCl ₂ , LiCl, NaOAc, CH ₃ CN	74%
6	PdCl ₂ , LiCl, Cu(OAc) ₂ (3.0 equiv), CH ₃ CN	94%
7	LiCl, AgOAc, CH ₃ CN	NR
8	AgOAc alone, CH ₃ CN	NR
9	Cu(OAc) ₂ alone, CH ₃ CN	NR
10	PdCl ₂ , LiCl, AgOAc, Toluene	8%
11	PdCl ₂ , LiCl, AgOAc, DMF	15%
12	PdCl ₂ , LiCl, AgOAc (1.0 equiv), CH ₃ CN	76%
13	PdCl ₂ , LiCl, AgOAc (0.1 equiv), CH ₃ CN	49%
14	PdCl ₂ (0.05 equiv), LiCl, AgOAc, CH ₃ CN	80%
15	PdCl ₂ (0.01 equiv), LiCl, AgOAc, CH ₃ CN	43%

[a] Unless otherwise noted, the reaction was carried out with **1a** (50 mg), Pd(II) catalyst (0.1 equiv), LiCl (2.0 equiv), AgOAc (3.0 equiv), in 2.5 mL CH₃CN at 80 °C for 24 h or until no more **1a** left monitored by TLC. [b] Yield of isolated product.

With an optimized reaction condition, we then prepared various unsaturated amides (**1b-m**, see the Supporting Information) to explore the substrate scope. As summarized in table 2, different $\alpha,\beta,\gamma,\delta$ -unsaturated nitriles (**3a-e**) and cinnamitriles (**3f-m**) were obtained in good to excellent yield. The reaction condition is compatible with many functional groups such as double bond, ketal protecting group, electron-donating ether and electron-withdrawing nitro group. Halogens including Cl, Br, and I are tolerated as well.

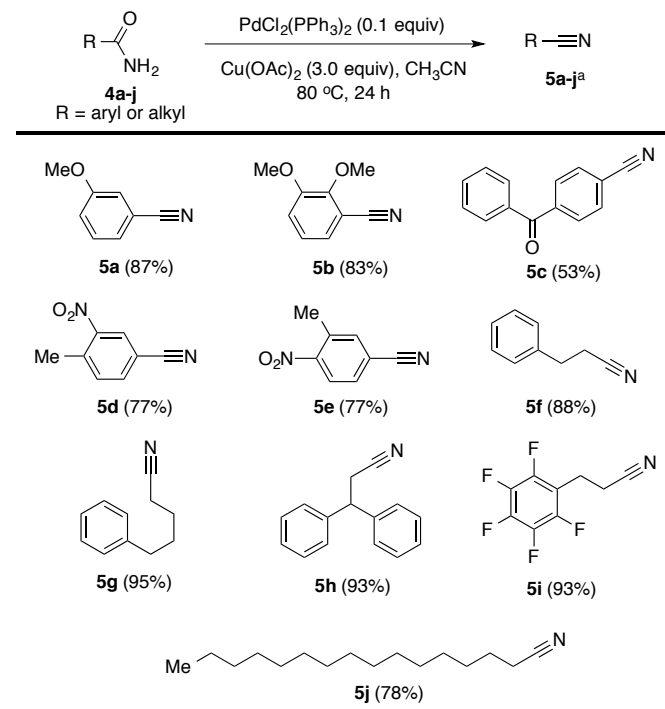
We then proceeded to expand the dehydration method to aromatic and aliphatic amides. To our surprise, the optimized reaction condition for unsaturated amides gave significantly reduced yield for the aromatic and aliphatic amides. We then quickly optimized the reaction condition and found that replacement of PdCl₂ and AgOAc with Pd(PPh₃)₂Cl₂ and Cu(OAc)₂ respectively has beneficial effect to these two type of amides. As shown in table 3, aromatic nitriles with methoxy (**5a-b**), ketone (**5c**), nitro and alkyl (**5d-e**) groups were produced in 53-88% yield. Aliphatic nitriles **5f-j** were obtained in good to excellent yield as well. For the cases of **4f** to **5f** and **4h** to **5h**, no C-H amination product was observed. Pentafluoroaryl group was tolerated as well (**5i**).

Table 2. Dehydration of unsaturated amides.



[a] Yield of isolated product.

Table 3. Dehydration of aryl and alkyl amides.



[a] Yield of isolated product.

Currently, the detailed reaction mechanism of this palladium-catalyzed dehydration of amides to nitriles remains unclear. Since

CH₃CN is critical for the dehydration and acetamide was produced with the desired nitriles in equal amount, the overall reaction process could be viewed as a palladium(II)-catalyzed “water shuffling” process between acetonitrile and the corresponding amide.^{6b} Additionally, in our case, acetate salt is indispensable for the high reaction yield. Other bases such as NaOH, KF, KOtBu, NaH, K₂CO₃, Na₂CO₃ and K₃PO₄ were ineffective. With these experimental observations we proposed that the internal acetate act as a base to promote both the formation of a mixed imidic anhydride, **B** (cf. **A**→**B**, Figure 1) and elimination from **B** to the corresponding nitrile and acetamide. Since CH₃CN was used as solvent, the reaction was driven to the right direction. Notably, the reversed reaction by using excess amount of acetamide was unsuccessful in our case.¹²

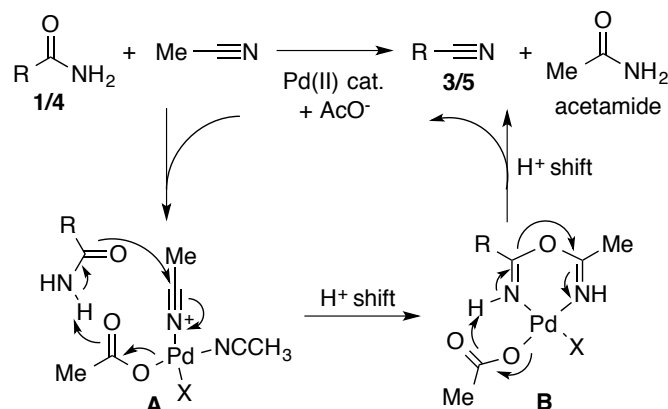


Figure 1. Proposed reaction mechanism.

Conclusions

In summary, an acetate-facilitated palladium-catalyzed synthesis of nitriles from amides was developed. Two similar, but complementary reaction conditions have been identified to convert various amides to nitriles in good to excellent yield with excellent functional compatibility. In particular, $\alpha,\beta,\gamma,\delta$ -unsaturated amides and cinnamides, which were not well studied in previous protocols, gave the corresponding nitriles smoothly and efficiently. More experiments are necessary to fully understand the reaction mechanism, which would provide new insights to palladium-catalyzed dehydration of amides or the reversed reaction.

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Notes and references

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Graphical Abstract

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