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Mild and Reversible Dehydration of Primary Amides with $PdCl_2$ in Aqueous Acetonitrile

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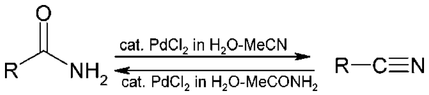
ABSTRACT



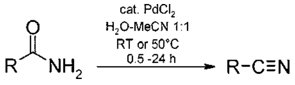
A new, mild, and reversible method to convert primary amides to nitriles in good yields using $PdCl_2$ in aqueous acetonitrile is described.

According to literature, phosphorus pentoxide,[1] titanium tetrachloride,[2] thionyl chloride,[3] and trifluoroacetic anhydride[4] are some reagents used to prepare nitriles through primary amide dehydration. In addition, more recently, methods using other reagents to perform the dehydration under milder conditions, such as PyBOP,[5] EDCI,[6] and cyanuric chloride,[7] have been reported. All of these methods are characterized by a common requirement, that is, the reaction must be performed under anhydrous conditions, in which the use of moisture-sensitive reagents is allowed and the formation of dehydrated product is favored.

Transition metal complexes have been reported in the literature as useful catalysts for different organic reactions. Although palladium(II) complexes have been known to be used in the hydrolysis of nitriles[8] to primary amides, the reverse reaction of dehydration has never been described.

In this article, we report the use of $PdCl_2$ to convert primary amides into the corresponding nitriles in aqueous organic solvents under mild conditions. It was found that by using $PdCl_2$ in water/acetonitrile as solvent mixture, primary amides dehydrated in good yields after a few hours at room temperature (Scheme 1).

Scheme 1



To better characterize this new process and its reaction parameters, further experiments were conducted.

Catalyst. A stoichiometric amount of $PdCl_2$ was first tested. Successive experiments (see Table 1) showed that a catalytic process could be accomplished with 0.1 equiv of $PdCl_2$ per mole of substrate. However, it was also noticed that an amount of $PdCl_2$ as low as 0.005 equiv could also lead to good conversion in an acceptable time frame (see Table 1, entries 3 and 4). In addition, we found that $PdCl_2$ could be replaced with $PdCl_2(MeCN)_2$ or $Pd(OAc)_2$ with similar results. However, when employing $Pd(OAc)_2$ instead of $PdCl_2$, although conversion and reaction speed were similar, the reaction solutions showed different pH. $PdCl_2$ generated reaction solutions with pH in the range 2.8−3.5, whereas $Pd(OAc)_2$ generated solutions with pH in the range 4.7−5. This was a useful finding, which indicated that $Pd(OAc)_2$ would be preferred for substrates particularly sensitive to an acidic environment.

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(1) Reisner, D. B.; Coring, E. G. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 144.

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(3) Krynitsy, J. A.; Carhart, H. W. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 436.

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(5) PyBOP: benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate. Bose, D. S.; Narsaiah, A. V. *Synthesis* **2001**, 373.

(6) EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide. Bose, D. S.; Sunder, K. S. *Synth. Commun.* **1999**, 4235.

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Table 1. Dehydration of Primary Amides with $PdCl_2$

entry	substrate (100 mg)	product	solvent	$PdCl_2$[a]	temp (°C)	time (h)	yield (%)[b]
1	Ph-$CONH_2$	PhCN	6 mL of H_2O/MeCN = 1:1	0.1	rt	4	91
2	Ph-$CONH_2$	PhCN	6 mL of H_2O/MeCN = 1:1	0.1	50	0.5	85
3	Ph-$CONH_2$	PhCN	6 mL of H_2O/MeCN = 1:1	0.005	50	4	68
4	Ph-$CONH_2$	PhCN	6 mL of H_2O/MeCN = 1:1	0.005	rt	16	74
5	2-NO_2-PhCONH$_2$	2-NO_2-PhCN	6 mL of H_2O/MeCN = 1:1	0.1	rt	16	93
6	2-NO_2-PhCONH$_2$	2-NO_2-PhCN	6 mL of H_2O/MeCN = 1:1	0.1	50	1	90
7	2-MeO-PhCONH$_2$	2-MeO-PhCN	6 mL of H_2O/MeCN = 1:1	0.1	rt	1	77
8	2-MeO-PhCONH$_2$	2-MeO-PhCN	6 mL of H_2O/MeCN = 1:1	0.1	50	0.5	70
9	2-HO-PhCONH$_2$	2-OH-PhCN	6 mL of H_2O/MeCN = 1:1	0.1	rt	4	91
10	2-HO-PhCONH$_2$	2-OH-PhCN	6 mL of H_2O/MeCN = 1:1	0.1	50	1	98
11	$FmocNHCH_2CONH_2$	$FmocNHCH_2CN$	6 mL of H_2O/MeCN = 1:1	0.1	rt	16	65[c]
12	Ph-$CONH_2$	PhCN	6 mL of MeCN	0.1	rt or 50	22	nd[d]
13	$FmocNHCH_2CONH_2$	$FmocNHCH_2CN$	6 mL of H_2O/DMF = 1:5	0.1	rt or 50	22	nd[d]
14	$FmocNHCH_2CONH_2$	$FmocNHCH_2CN$	6 mL of H_2O/MeOH = 1:5	0.1	rt	22	nd[d]
15	1-NaphthylCH$_2$CONH$_2$	1-naphthylCH$_2$CN	9 mL of H_2O/MeCN = 1:1	0.1	rt	16	80

[a] Equivalents of $PdCl_2$ per mole of substrate. [b] If not specified yield is calculated by HPLC analysis by comparison with authentic samples. [c] Isolated yield. [d] Not detected

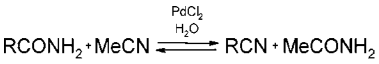
Solvent. The use of acetonitrile as a solvent appeared to be critical for the dehydration reaction. Indeed, when the reaction was performed without acetonitrile as a cosolvent, there was no formation of the desired nitrile (Table 1, entries 13 and 14). Unexpectedly, the presence of water was also found to be essential. In fact, the reaction conducted in acetonitrile only (see Table 1, entry 12) did not show any formation of nitrile either. Therefore, a mixture of water and acetonitrile is needed in this process. The ratio of water/acetonitrile can be adapted depending on the substrate solubility. In addition, a third solvent such as MeOH, THF, or DMF can be added, if necessary, without interfering the reaction.

Atmosphere. The reaction usually has been conducted in air. However, an inert atmosphere can be employed if required.

Substrate. The reaction gave satisfactory results on both aliphatic and aromatic primary amides, and in the latter case, electronic-withdrawing or -donating groups did not significantly affect the reaction rate.

The reaction was shown to be reversible, and water was found to be formally transferred from the substrate to the acetonitrile (Scheme 2).

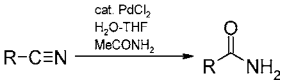
Scheme 2



To highlight this transfer, an experiment in which PhCN was used as a cosolvent, instead of MeCN, was carried out. HPLC analysis then followed. In this experiment, formation of $PhCONH_2$, due to benzonitrile hydration, was observed concurrently with the dehydration of the desired primary amide.

As a result of the reversibility of this reaction process, nitriles can be hydrated to primary amides (Scheme 3) with a similar procedure by simply replacing acetonitrile with a primary amide, thus shifting the equilibrium of Scheme 2 in the left direction. For semplicity, we decided to use acetamide, while THF was added as a cosolvent to obtain a homogeneous solution.

Scheme 3



Indeed, $PhCONH_2$ was completely produced in 6 h at room temperature from PhCN (1 mmol) in THF/water = 3:1 (4 mL) with $PdCl_2$ (0.1 equiv/mol of substrate) by using $MeCONH_2$ (250 mg) to force the hydration process. In the case of aliphatic nitriles the hydration process was slower but still efficient (1-naphthylacetonitrile in the same conditions gave 90% of conversion after 22 h and 4-phenyl-1-butylnitrile gave 53% of conversion after 22 h).

Mechanism. Experiments aimed to study the mechanism have not yet been accomplished. Palladium salt might be involved in this “water transfer” similarly to the transferhydrogenation process (H-transfer).[9] Nevertheless, in our case, the water role should be clarified to allow a complete and correct mechanicistic description of the reaction. Considering the available data, the formation of an intermediate complex similar to **A** (Scheme 4) might be hypotized. Thus, the reversibility of the reaction might be explained considering that the complex **A** could evolve in two directions depending on the presence of a large amount of acetonitrile (dehydration process) or acetamide (hydration process). However, the clarification of the final mechanism deserves further studies.

In conclusion, the new procedure described in this article offers a useful alternative to other known methods of primary

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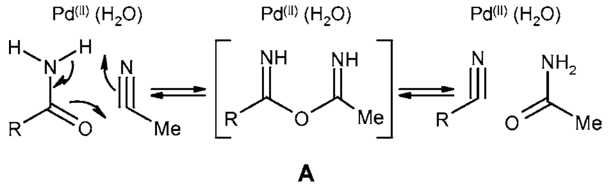
Scheme 4



amide dehydration. In addition, it is of special value in providing the possibility to work with an aqueous solvent, which is generally preferable in case of hydrophilic natural compounds and for applications in green chemistry processes. Finally, the observed reversibility also makes the process appealing as a new protecting group for the primary amide moiety.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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