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Anhydrous Hydration of Nitriles to Amides using Aldoximes as the Water Source

Jinwoo Lee, Min Kim, Sukbok Chang,* and Hee-Yoon Lee*

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Korea

leeheeyoon@kaist.ac.kr; sbchang@kaist.ac.kr

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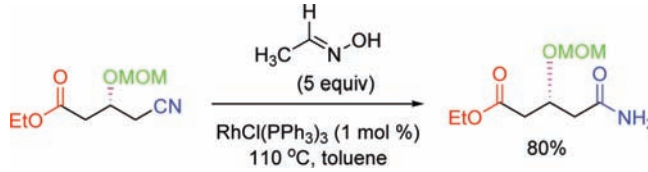
ABSTRACT



Anhydrous hydrolysis of nitriles to amides was developed using acetaldoxime as the water source in the presence of Rh catalyst. Conversion of various nitriles to amides was performed under neutral and anhydrous conditions, and the reaction displays excellent compatibility with acid or base labile and hydrolytically labile functional groups.

Nitrile is one of the most versatile functional groups as it can be readily transformed into various other functional groups or reactive intermediates. Among them, hydration of nitriles has great synthetic significance in the preparation of the corresponding amides for the *isohypsic* nature of the transformation that is an important factor in redox-economy in organic synthesis[1] and for its broad industrial and pharmacological applications.[2] For example, hydration of acrylonitrile produces annually more than 2×10^5 tons of acrylamide and is the most important technology for the production of this chemical.[3] The reaction proceeds in a sequence of distinct steps upon treatment with strong inorganic acids or bases. Due to these harsh conditions, carboxylic acids could form as the major byproduct, and more importantly, acid or base labile functional groups and protective groups cannot be tolerated.[4] Although metals, especially transition metal catalyzed nitrile hydrolysis reactions, have offered mild reaction conditions and selective formation of amides without the formation of carboxylic acids, functional group tolerability during the nitrile hydrolysis has not been addressed yet.[5] Therefore, the development of an efficient and mild process for the synthesis of amides from nitriles even in the presence of other labile functional groups would be a valuable tool in organic synthesis.

Herein, we report a selective hydrolysis reaction of nitriles to amides under essentially neutral and anhydrous conditions

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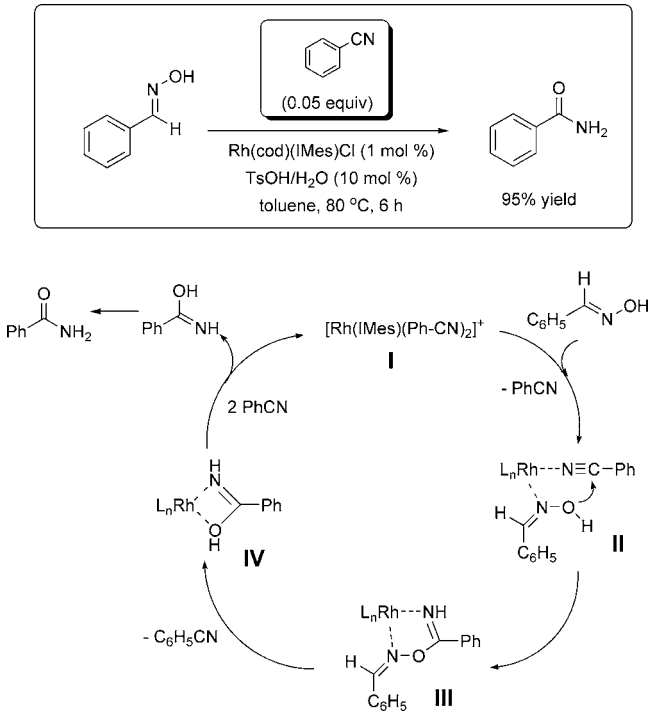
that allow other functional groups to remain intact. During the development of mild reaction conditions for the Rh-catalyzed transformation of aldoximes into amides,[6] we observed an interesting additive effect. Development of the anhydrous hydration reaction of nitriles to amides was based on mechanistic insight from our recent report of the Rh-catalyzed rearrangement of aldoximes into amides (Scheme 1).[7]

Scheme 1. Mechanistic Proposal for the Nitrile-Mediated Amide Formation

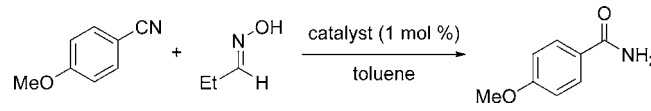


In our previous report, we found out that Rh-catalyzed rearrangement of aldoximes to amides was accelerated by the nitrile additives. It was proposed that the added nitriles cooperatively catalyze the dehydration reaction of aldoximes into the corresponding nitriles, while the hydroxyl group of aldoximes is taken up by the nitriles to form amides. In fact, it was observed that the total concentration of nitriles remained constant throughout the reaction course.[7] This mechanistic feature that required the formation of the aldoxime−nitrile−metal complex such as **II** prompted us to conceive an idea that aldoximes could serve as the water source for the hydration of nitriles, thus excluding water from the hydration reaction completely.[8]

During the Rh-catalyzed rearrangement of aldoximes to amides, aliphatic aldoximes were found to be not as much influenced by the added corresponding nitriles as aryl aldoximes.[7] This result could imply that aliphatic nitriles would bind to the catalyst less tightly than aromatic nitriles, implying that aliphatic nitriles may not effectively participate in the rearrangement of aldoximes into amides. This observation led us to speculate a possibility of utilizing *aliphatic aldoxime as the water source for the "anhydrous" hydration of nitriles.* If an aliphatic aldoxime was used as the hydrating agent for nitriles, aromatic nitriles could be hydrated effectively by the rhodium catalyst while utilizing aliphatic aldoximes as the hydrating species since the in situ generated aliphatic nitriles during the reaction course would not compete with aromatic nitriles for the subsequent hydration.

The anhydrous hydration of nitriles was first examined with 4-methoxybenzonitrile as a test substrate using propionaldoxime as a stoichiometric hydrating species (Table 1).

Table 1. Screen of Reaction Conditions[a]



entry	catalyst	additive	temp (°C)	convn (%)[b]
1	RhCl(IMes)(cod)	*p*TsOH/H_2O	80	48
2	RhCl(IMes)(cod)	*p*TsOH/H_2O	110	72
3	RhCl(IMes)(cod)	−	110	78
4	RhCl(IMes)(cod)	−	80	57
5	RhCl(IMes)(cod)	−	110	87[c]
6	$RhCl(PPh_3)_3$	−	110	80
7	$RhCl(PPh_3)_3$	−	110	89[c]

[a] Reaction conditions: a solution of 4-methoxybenzonitrile (0.5 mmol), propionaldoxime (1.5 mmol), Rh catalyst (1.0 mol %), and additive (10 mol %) in toluene (0.125 mL) was stirred for 6 h in a reaction vial (1 mL). [b] Measured from ^1H NMR spectra of the crude products. [c] 2.5 mmol of propionaldoxime was used. IMes = *N*,*N*-bis(2,4,6-trimethylphenyl)imidazole ligand.

The reaction was first tested under reaction conditions similar to those used in the rearrangement of aldoximes into amides (entry 1).[7] Quite contrary to our expectation based on the mechanistic speculation,[8a] it turned out that the conversion of nitriles to amides was much slower than the rearrangement of aldoximes into amides. Higher reaction temperatures were required to accelerate the hydration reaction (entry 2). To our surprise, *p*-toluensulfonic acid that accelerated the rearrangement of aldoximes into amides[7] did not affect the hydration reaction efficiency (compare entries 2 and 3). This result strongly implies that the role of *p*-toluensulfonic acid during the rearrangement of aldoximes into amides might have been helping a competitive coordination of a nitrile to the catalyst,[8a] in addition to the activation of the catalyst.[7] In consequence, the existence of a large amount of a nitrile seemed to abolish the effect of the

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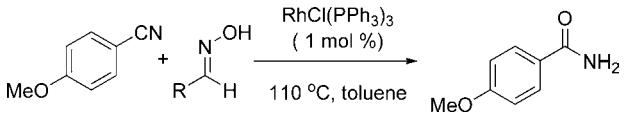
(8) For detailed mechanistic and kinetic study in support of the intermediate **II** with Pd and application to the hydration of nitriles, see: (a) Leusink, A. J.; Meerbeek, T. G.; Noltes, J. G. *Recl. Trav. Chim. Pays-Bas.* **1976**, *95*, 142–145. (b) Kim, E. S.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2973–2975.

p-toluensulfonic acid additive. This unanticipated result ensures the neutrality as well as the anhydrous nature of the reaction.

When the amount of propionaldoxime was increased, conversion of the hydration reaction was consequently improved (entry 5). Since propionitrile generated from the dehydration process of propionaldoxime could compete with 4-methoxybenzonitrile, an extra amount of aldoxime was required to improve the conversion and the reaction rate. Contrary to the Rh-catalyzed rearrangement of aldoximes to amides,[7] commercially available Wilkinson's catalyst worked as well as Rh(NHC) catalyst (entries 6 and 7).

The effect of aldoxime substituents on the hydration reaction was next explored with the expectation that the bulkiness of the substituent could affect reaction rate of the hydration reaction as it could alter the rate of the dehydration reaction of aldoximes and the rate of hydration of nitriles produced from aldoximes (Table 2).

Table 2. Substituent Effect on Hydration Reactions[a]



entry	R	aldoxime (equiv)	time (h)	convn (%)[b]
1	Me	1.0	6.0	46
2	Me	3.0	6.0	83
3	Me	5.0	0.5	93
4	Me	5.0	1.5	93
5	*t*-Bu	1.5	1.0	77
6	*t*-Bu	1.5	2.0	88
7	*t*-Bu	2.0	2.0	95

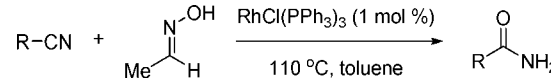
[a] Reaction conditions: a solution of 4-methoxybenzonitrile (0.5 mmol), aldoxime, and Rh catalyst (1.0 mol %) in toluene (0.125 mL) was stirred in a reaction vial (1 mL). [b] Measured from the ^{1}H NMR spectra of the crude products.

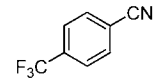
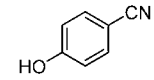
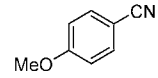
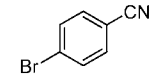
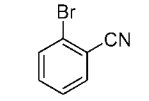
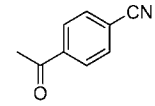
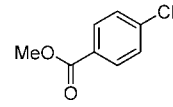
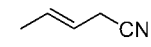
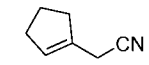
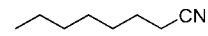
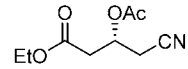
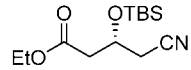
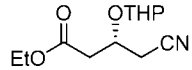
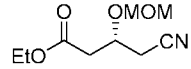
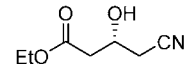
While acetaldoxime showed a result similar to propionaldoxime (entry 1), higher concentration of acetaldoxime not only improved the conversion but also accelerated the hydration reaction substantially (entry 2). No significant improvement of the conversion even after an extended reaction time (entry 3) indicated that the conversion of acetonitrile into acetamide becomes the dominant reaction pathway when most nitrile substrate was consumed.

When sterically encumbered pivalaldoxime was used as a hydrating agent, the conversion rate was similar to other cases (entry 4), and extended reaction time further improved the conversion (entry 5). When 2.0 equiv of pivalaldoxime was used, the hydration reaction was completed in 2 h (entry 6). This result indicates that the bulky aldoxime may play a role as a better hydrating agent as the bulkiness might prevent hydration of the corresponding nitrile in situ generated from the aldoxime.

Although bulky aldoxime has an advantage as a hydrating agent, we chose acetaldoxime as the hydrating reagent for practical reasons. Acetaldoxime was commercially available and made the purification of the hydration product simple as acetamide byproduct was readily soluble in water.

Table 3. Hydration of Various Nitriles Using Acetaldoxime[a]



entry	nitrile	yield[b]
1		95
2		99
3		79
4		96
5		90
6		87
7		78
8		81
9		82
10		92
11		81
12		76
13		75
14		80
15[c]		99

[a] Reaction conditions: a solution of nitrile (0.5 mmol), acetaldoxime (2.5 mmol), and Rh catalyst (1.0 mol %) in toluene (0.125 mL) was stirred in a reaction vial (1 mL) for 4−5 h. [b] Isolated yield. [c] Pivalaldoxime (2.0 equiv) was used.

The new protocol of anhydrous hydration was subsequently applied to various aromatic nitriles and aliphatic nitriles. A complete conversion of nitriles to amides took place within 4−5 h at 110 °C in toluene using 1 mol % of Wilkinson's catalyst and 5 equiv of acetaldoxime. Aromatic nitriles were smoothly hydrated to give the corresponding amides in excellent yields under the employed reaction conditions. The hydration proceeded effectively for various benzonitriles substituted with either electron-withdrawing or electron-donating groups (entries 1−4, Table 3). *Ortho*-substituted benzonitriles also showed high reactivity providing excellent yield (entry 5). Then, we examined hydration reaction with derivatives of benzonitriles containing ketone or ester groups. In both cases, nitriles were hydrated effectively without any side products derived from potential reactions of those carbonyl groups (entries 6 and 7). We were pleasantly surprised by the observation that, in addition to aryl nitriles, aliphatic substrates were also hydrated with excellent efficiency (entries 8−10). Use of 5 equiv of acetaldoxime appeared not only to facilitae the reaction rate but also to provide enough reagent for aliphatic nitriles to overcome competing hydration of acetonitrile generated from acetaldoxime. Results from entries 7, 8, and 9 clearly demonstrate that the reaction is not only anhydrous but also neutral, and the reaction can be applied to various compounds with sensitive functional groups or protecting groups which are easily deprotected under acidic or basic media (entries 11−15). In addition to that, no racemization during the reaction was observed.[9]

In summary, we have developed a new "anhydrous" and "neutral" protocol for the hydration of nitriles to amides in good yield using commercially available acetaldoxime and Wilkinson's catalyst. Under the new protocol, compounds with acid or base sensitive functional and protecting groups along with other sensitive compounds such as acrylonitrile or heterocyclic nitriles that were reported to be converted into amides in the previous reports[7,8b] could be tolerated, thus giving a wide opportunity that the developed synthetic method can find numerous applications in organic synthesis and process chemistry.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Stereochemical integrity of the product in the entry 15 was confirmed through Mosher ester formation as no isomeric compound was observed.