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An efficient $InCl_3$-catalyzed hydration of nitriles to amides: acetaldoxime as an effective water surrogate

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ABSTRACT

An efficient $InCl_3$-catalyzed hydration protocol of nitriles to amides was developed. The reaction was carried out in toluene at refluxing temperature with the aid of acetaldoxime as an effective water surrogate to produce amides in high yields.

Hydration of nitriles to the corresponding amides is an important transformation from both academic and industrial points of view.[1] Classically the reaction was carried out in the presence of a strong acid or base catalyst, but these methods suffer from two major drawbacks, drastic conditions and over-hydrolysis to carboxylic acid, in most cases.[2] Transition-metal complex-assisted activation of nitrile can enhance the rate of hydration and avoid the use of a drastic condition. Various metal catalysts including Ru,[3a–d] Rh,[3e,h] Ag,[3f] Ni,[3g], and Pd[4] have been reported as effective in organic and/or aqueous medium.[3,4] Recently, a Pd-catalyzed hydration of nitrile to amide was developed by us using acetaldoxime.[4]

During our recent studies of Pd-catalyzed conversion of nitrile to amide,[4] we used acetaldoxime as a water surrogate. The weakly activated nitrile by a palladium catalyst can be attacked easily by acetaldoxime to produce amide and acetonitrile as a by-product. We reasoned out that replacement of a palladium catalyst with an easily accessible Lewis acid can increase the applicability of the hydration method. The Lewis acid catalyst has to activate the nitrile efficiently and at the same time does not deactivate the nucleophilicity of acetaldoxime in order to deliver efficiently the water molecule from acetaldoxime to nitrile.[5] Screening of catalysts was carried out in the reaction of benzonitrile in toluene in the presence of acetaldoxime, as shown in Table 1. The use of $InCl_3$ (entries 1–4) or $InBr_3$ (entry 7) was found to be effective and produced benzamide in excellent yields. The reaction at room temperature required a long reaction time (entry 2). As in entry 5, benzamide was not formed without acetaldoxime even after 20 h. The reaction was very slow without $InCl_3$; however, we could obtain benzamide in 52% after 2 days (entry 6). The use of other catalysts such as $FeCl_3$, BF_3, and $ZrCl_4$ (entries 8–10) were ineffective. Moreover, the addition of these catalysts was even found to be harmful (compare, entry 6 and entries 8–10). Thus we chose the conditions in entry 3 as the best one.

As shown in Table 2, various nitriles including aromatic nitriles having electron-donating or electron-withdrawing substituents (entries 1–6), alkenenitriles (entries 7 and 8), aliphatic nitriles (entries 9 and 10), and heterocyclic nitriles (entries 11 and 12) were converted into the corresponding amides in good to excellent yields.[6] It is interesting to note that phthalimide was formed as

Table 1
Screening of conditions for the hydration of benzonitrile (**1a**) to benzamide (**2a**)

Entry	Conditions	**2a** (%)
1	$InCl_3$ (10 mol %), $CH_3CH{=}NOH$ (3.0 equiv), toluene, reflux, 3 h	7
2	$InCl_3$ (5 mol %), $CH_3CH{=}NOH$ (3.0 equiv), toluene, rt, 4 days	87
3	$InCl_3$ (5 mol %), $CH_3CH{=}NOH$ (3.0 equiv), toluene, reflux, 3 h	98
4	$InCl_3$ (5 mol %), $CH_3CH{=}NOH$ (2.0 equiv), toluene, reflux, 12 h	96
5	$InCl_3$ (5 mol %), no $CH_3CH{=}NOH$, toluene, reflux, 20 h	0
6	No $InCl_3$, $CH_3CH{=}NOH$ (3.0 equiv), toluene, reflux, 2 days	52
7	$InBr_3$ (5 mol %), $CH_3CH{=}NOH$ (3.0 equiv), toluene, reflux, 3 h	98
8	$FeCl_3$ (10 mol %), $CH_3CH{=}NOH$ (3.0 equiv), toluene, reflux, 2 days	25
9	BF_3 etherate (10 mol %), $CH_3CH{=}NOH$ (3.0 equiv), toluene, reflux, 15 h	33
10	$ZrCl_4$ (10 mol %), $CH_3CH{=}NOH$ (3.0 equiv), toluene, reflux, 2 days	19

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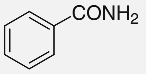
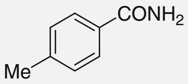
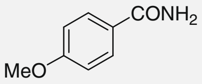
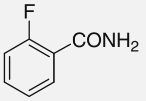
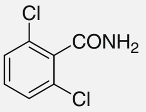
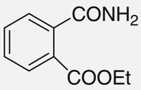
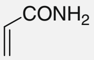
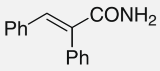
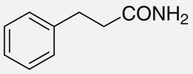
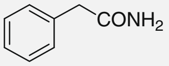
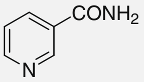
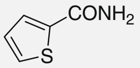
Table 2
Hydration of various nitriles **1a**–**l** to the amides **2a**–**l**[a]

Entry	Product (%)
1	 **2a** (3 h, 98)
2	 **2b** (3 h, 98)
3	 **2c** (4 h, 96)
4	 **2d** (5 h, 99)
5	 **2e** (5 h, 95)
6	 **2f** (6 h, 13)[b]
7	 **2g** (24 h, 73)[c]
8	 **2h** (24 h, 86)
9	 **2i** (4 h, 85)
10	 **2j** (5 h, 92)
11	 **2k** (5 h, 98)
12	 **2l** (5 h, 99)

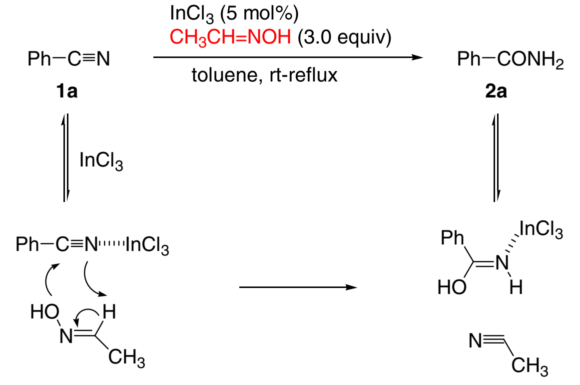
[a] Conditions: nitrile (1.0 mmol), $CH_3CH{=}NOH$ (3.0 mmol), $InCl_3$ (5 mol %), reflux, time in parenthesis.
[b] Phthalimide (**2f′**) was isolated in 71%.
[c] Run at room temperature.

the major product via a $InCl_3$-catalyzed cyclization of **2f** (entry 6). The reaction of acrylonitrile failed completely under the refluxing conditions and produced polymeric materials to the contrary to our previous Letter using a palladium catalyst.[4a,7] However, we obtained acrylamide in 73% at room temperature (entry 7). The reaction of α-phenylcinnamonitrile (**1h**) produced **2h** under refluxing conditions (entry 8) without the formation of polymeric materials.

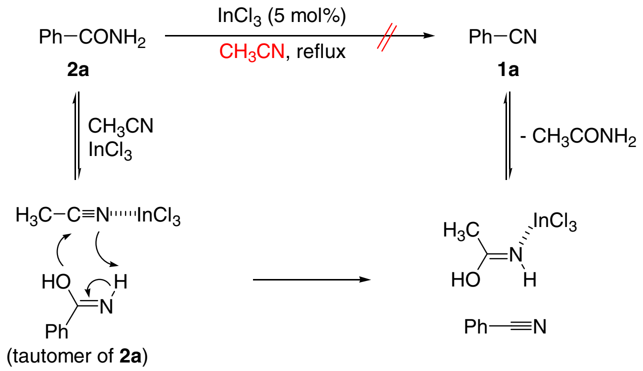
The plausible reaction mechanism could be proposed as shown in Scheme 1. Hydroxyl group of acetaldoxime moved to the carbon atom of benzonitrile which was activated with $InCl_3$ to produce benzamide and acetonitrile, as in our previous Pd-catalyzed hydration papers.[4a,b] In the meantime we found an interesting paper of Sandhu and co-workers, which described the dehydration of aldoxime to nitrile catalyzed by $InCl_3$ in acetonitrile.[8a] We think the use of acetonitrile as a solvent must be crucial although they did not mention this important point.[8a] The result is exactly matched with our rationale and catalyst-screening results in Table 1, coincidently. In addition, trichloroacetonitrile has been known as an efficient dehydrating agent for aldoxime to nitrile,[8b] and this method also implied the similar concept to ours (Scheme 1).

Conversion of amide to nitrile is also an important chemical transformation, and various dehydration methods are used for this purpose involving the use of $SOCl_2$, P_2O_5, $POCl_3$, and $COCl_2$, as some examples.[9] Conversion of amide to nitrile via the corresponding six-membered transition state with a metal oxide such as stannyl oxide[10a] or rhenium(VII) oxo complex[10b] has also been reported. Thus, we examined the reaction of benzamide in acetonitrile in the presence of $InCl_3$. As in Scheme 2, if the tautomer of benzamide can react with the activated acetonitrile, then we could obtain benzonitrile and a by-product, acetamide. However, the reaction failed completely presumably due to low nucleophilicity of benzamide tautomer.

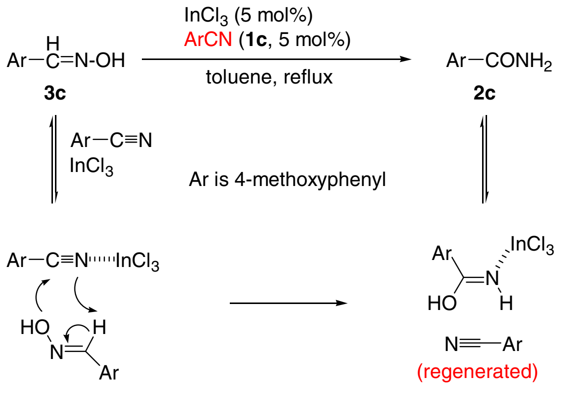
As a next examination, we imagined the feasibility of one-pot conversion of aldoxime to amide. Although the conversion can be carried out indirectly via a sequential dehydration to nitrile and a subsequent hydration to amide, the development of a direct one-pot method is highly meaningful.[11] Thus, we examined the reaction of 4-methoxybenzaldoxime (**3c**), as a typical example, in the presence of $InCl_3$ (5 mol %) and a catalytic amounts of



Scheme 1.

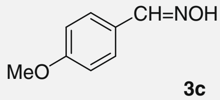
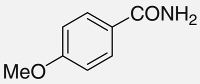
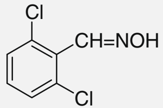
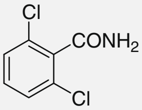
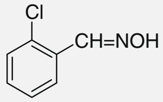
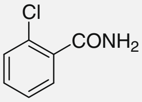
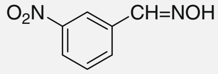
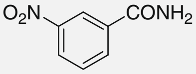


Scheme 2.



Scheme 3.

Table 3
One-pot conversion of aldoximes to amides

Entry	Aldoxime[a]	Conditions	Amide (%)
1	 **3c**	InCl$_3$ (5 mol %), **1c** (5 mol %) toluene, reflux, 18 h	 **2c** (91)
2	 **3e**	InCl$_3$ (5 mol %), **1e** (5 mol %) ODCB, reflux, 15 h	 **2e** (94)
3	 **3m**	InCl$_3$ (5 mol %), **1m** (5 mol %) ODCB, reflux, 16 h	 **2m** (91)
4	 **3n**	InCl$_3$ (5 mol %), **1n** (5 mol %) ODCB, reflux, 16 h	 **2n** (93)[b]

[a] The configuration of oxime is *E* (>95%).[4c]
[b] Yield of **2n** was 65% when toluene was used (24 h).

4-methoxybenzonitrile (**1c**, 5 mol %). Once the reaction started via the similar mechanism involving a six-membered transition state (Scheme 3), then 4-methoxybenzonitrile can be regenerated and the catalytic cycle will go to completion. A similar concept was also applied in the Rh-catalyzed conversion of amide to nitrile studied by Chang and co-workers.[11c] Desired 4-methoxybenzamide (**2c**) was isolated in 91% yield (entry 1 in Table 3).[12] However, the reaction of 2,6-dichlorobenzaldoxime (**3e**) in the presence of 2,6-dichlorobenzonitrile (**1e**, 5 mol %) did not afford 2,6-dichlorobenzamide (**2e**) in toluene. Fortunately, **2e** was obtained in 94% yield when we heated the reaction mixture in *o*-dichlorobenzene (ODCB) for 15 h. The results of one-pot conversion of aldoximes into amides are summarized in Table 3.

In summary, we disclosed an efficient method for the hydration of nitrile to amide catalyzed by InCl$_3$ with the aid of acetaldoxime. In addition, a one-pot conversion method of aldoxime to amide was developed by using a similar concept.

Acknowledgment

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References and notes

1. (a) Thallaj, N. K.; Przybilla, J.; Welter, R.; Mandon, D. *J. Am. Chem. Soc.* **2008**, *130*, 2414–2415; (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. p. 1988; (c) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771–1802. and further references cited therein; (d) Bokach, N. A.; Kukushkin, V. Y. *Russ. Chem. Rev.* **2005**, *74*, 153–170; (e) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1–21.
2. For the hydration of nitriles to amides catalyzed by acid or base, see: (a) Moorthy, J. N.; Singhal, N. *J. Org. Chem.* **2005**, *70*, 1926–1929. and further references cited therein; (b) Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, 949–950; (c) Kopylovich, M. N.; Kukushkin, V. Y.; Haukka, M.; Frausto da Silva, J. J. R.; Pombeiro, A. J. L. *Inorg. Chem.* **2002**, *41*, 4798–4804; (d) Hall, J. H.; Gisler, M. *J. Org. Chem.* **1976**, *41*, 3769–3770; (e) Sharghi, H.; Sarvari, M. H. *Synth. Commun.* **2003**, *33*, 207–212; (f) Berrien, J.-F.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1994**, *59*, 3769–3774; (g) McIsaac, J. E., Jr.; Ball, R. E.; Behrman, E. J. *J. Org. Chem.* **1971**, *36*, 3048–3050; (h) Merchant, K. J. *Tetrahedron Lett.* **2000**, *41*, 3747–3749.
3. For the metal-assisted hydration of nitrile to amide, see: (a) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Eur. J.* **2008**, *14*, 6601–6605; (b) Polshettiwar, V.; Varma, R. S. *Chem. Eur. J.* **2009**, *15*, 1582–1586; (c) Yi, C. S.; Zeczycki, T. N.; Lindeman, S. V. *Organometallics* **2008**, *27*, 2030–2035; (d) Leung, C. W.; Zheng, W.; Zhou, Z.; Lin, Z.; Lau, C. P. *Organometallics* **2008**, *27*, 4957–4969; (e) Goto, A.; Endo, K.; Saito, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3607–3609; (f) Mitsudome, T.; Mikami, Y.; Mori, H.; Arita, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2009**, 3258–3260; (g) Crestani, M. G.; Arevalo, A.; Garcia, J. *Adv. Synth. Catal.* **2006**, *348*, 732–742; Very recently, Chang and co-workers reported an efficient Rh-catalyzed hydration of nitrile to amide with aldoxime as a water surrogate as in our Pd-catalyzed hydration with acetaldoxime,[4] see: (h) Lee, J.; Kim, M.; Chang, S.; Lee, H.-Y. *Org. Lett.* **2009**, *11*, 5598–5601.
4. For our recent papers on Pd-catalyzed hydration of nitrile to amide, see: (a) Kim, E. S.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2973–2975; (b) Kim, E. S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 6286–6289; For the Pd-catalyzed dehydration of aldoxime to nitrile, see: (c) Kim, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1717–1719.
5. For the examples of preferential activation of electrophiles in the presence of aldoxime derivatives, see: (a) Yarovenko, V. N.; Taralashvili, V. K.; Zavarzin, I. V.; Krayushkin, M. M. *Tetrahedron* **1990**, *46*, 3941–3952; (b) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2001**, *42*, 6719–6722; (c) Moustafa, A. H. *Synthesis* **2003**, 837–840.
6. Typical experimental procedure for the hydration of benzonitrile: A stirred solution of **1a** (103 mg, 1.0 mmol), acetaldoxime (177 mg, 3.0 mmol), and InCl$_3$ (11 mg, 5 mol %) in toluene (1 mL) was heated to reflux for 3 h. After removal of the solvent the residue was separated by column chromatographic purification process (hexanes/EtOAc = 2:1) to afford benzamide, 119 mg (98%) as a white solid. In addition, acetamide was isolated together, 34 mg (19% based on acetaldoxime).
7. The reaction of acrylonitrile in the presence of $CH_3CH{=}NOH/InCl_3$ in aqueous EtOH (80 °C, 4 h) showed the formation of some polymeric materials and acrylamide was isolated in only 45%, whereas the reaction in the presence of $CH_3CH{=}NOH/Pd(OAc)_2/PPh_3$ in toluene (80 °C, 4 h) produced good yield (89%) of acrylamide without the formation of polymeric materials.[4a] The results stated that the formation of polymeric materials must be ascribed to the use of indium catalyst.
8. (a) Barman, D. C.; Thakur, A. J.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **2000**, 1196–1197; (b) Ho, T.-L.; Wong, C. M. *J. Org. Chem.* **1973**, *38*, 2241–2242.
9. For the classical dehydration methods of amide to nitrile and conversion of aldoxime to amide, see: (a) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1989; (b) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001.
10. (a) Bose, D. S.; Jayalakshmi, B. *J. Org. Chem.* **1999**, *64*, 1713–1714; (b) Ishihara, K.; Furuya, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2983–2986.
11. For the conversion of aldoxime to amide, see: (a) Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Yamaguchi, K.; Mizuno, N. *Chem. Asian J.* **2008**, *3*, 1715–1721; (b) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5202–5205; (c) Kim, M.; Lee, J.; Lee, H.-Y.; Chang, S. *Adv. Synth. Catal.* **2009**, *351*, 1807–1812; (d) Park, S.; Choi, Y.-a.; Han, H.; Yang, S. H.; Chang, S. *Chem. Commun.* **2003**, 1936–1937; (e) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 73–75; (f) Field, L.; Hughmark, P. B.; Shumaker, S. H.; Marshall, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 1983–1987.
12. Trace amounts of **1c** remained and it was removed by column chromatography. When we run the reaction of **3c** in the presence of acetonitrile (2–3 drops) instead of **1c**, the reaction was sluggish and **2c** was isolated in 60% (40 h). Without acetonitrile or **1c**, the reaction was very sluggish to produce **2c** in 35% (40 h). In addition, the reaction of **3c** in the presence of **1c** (5%) afforded 10–15% of **2c** even in *o*-dichlorobenzene (180 °C) for 18 h without InCl$_3$.