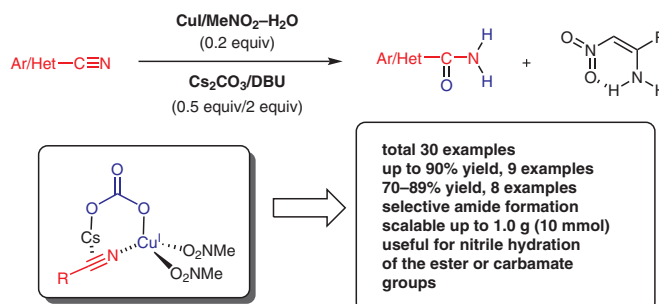


Nitrile Hydration Reaction Using Copper Iodide/Cesium Carbonate/DBU in Nitromethane–Water

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Abstract The catalytic nitrile hydration (amide formation) in a copper iodide/cesium carbonate/1,8-diazabicyclo[5.4.0]undec-7-ene/nitromethane–water system is described. The protocol is robust and reliable; it can be applied to a broad range of substrates with high chemoselectivity.

Key words catalysis, copper iodide, nitrile hydration, nitromethane–water, primary amides

Primary amides are one of the most important functional groups found in nature and used in scientific, pharmaceutical, and agrochemical industries.¹ In particular, the functionality of primary amides is critical to develop clinical drugs and their candidates, such as atenolol, temozolomide, pyrazinamide, piracetam, and levetiracetam.²

In 2005, amide formation was identified as the most complicated synthesis in the pharmaceutical industry by the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR).³ Due to recent advancements in the catalytic chemistry, nitrile hydration is recognized as a straightforward and atom-economical process¹ rather than as a traditional method.⁴ Traditional nitrile hydration using acid or base causes overhydrolysis or formation of byproducts because of the harsh reaction conditions (over 140 °C) such as high pressure or temperature. Recent advancements enable using homogenous and heterogeneous catalysts for mild and selective nitrile hydration. Metal-catalyzed nitrile hydration using Ru,⁵ Cu,⁶ Mn,⁷ Ni,⁸ Pd,⁹ Mo, Pt,¹⁰ Au,¹¹ Ag,^{11c} and Ce¹² catalysts was performed in an environmentally friendly aqueous medium. In particular, flow chemistry for nitrile hydration has been found to be an excellent in viewpoint of quantitative yields, scalability, and compatibility of functional groups.^{2d} On the other

hand, Williams and co-workers reported the mild and general procedure for nitrile hydration to amides using copper(II) acetate/*N,N*-diethylhydroxylamine at 35 °C.¹³ Aside from a couple of exceptions, most of the methods require high temperature and expensive catalysts. Therefore, catalytic nitrile hydration is now an attractive field in the synthetic organic chemistry. Furthermore, copper-catalyzed nitrile hydration is rarely reported compared with other metal-catalyzed nitrile hydrations.⁶ Recently, we reported the aza-Henry reaction of nitriles using copper iodide/cesium carbonate/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in nitromethane, which directly yielded 2-aminonitroalkenes upon the addition of nitromethane to the nitriles under nonaqueous conditions. However, the aza-Henry reaction in the presence of a small amount of water preferentially yielded the corresponding amides.¹⁴ These findings encouraged us to examine nitrile hydration using copper iodide/cesium carbonate/DBU in nitromethane–water. Herein, a novel nitrile hydration with high functional compatibility is reported.

We selected tolunitrile in order to screen the reaction conditions for nitrile hydration. First, we presented an example optimized as the aza-Henry reaction conditions of tolunitrile using copper iodide/Cs₂CO₃/DBU in MeNO₂ (Table 1, entry 1). Herein, we changed the conditions of the reaction medium for nitrile hydration from nonaqueous conditions used in the aza-Henry reaction to slightly aqueous conditions. In entry 2 (Table 1), **1a** was reacted with 1 equiv of copper iodide, 3 equiv of DBU, and 1 equiv of cesium carbonate in nitromethane–water (1:10) at 100 °C. The desired toluamide **2a** was obtained in 92% yield. Next, the optimization of each reagent was examined for the catalytic nitrile hydration. Similar conditions were used, including 0.2 equiv of copper iodide in nitromethane–water (10:1) in the presence of tetrabutylammonium hydrogensulfate at room temperature. However, the yield of **2a** was low (Table 1, en-

try 3). To determine the best ratio of nitromethane–water, we performed nearly identical experiments using different ratios of nitromethane–water (Table 1, entries 3–6). Based on these results, both nitromethane and water were deemed necessary to complete the nitrile hydration under the copper iodide/cesium carbonate/DBU system. After fixing the solvent ratio as 1:10 (nitromethane–water), the quantities of bases were examined (Table 1, entries 7–13). When the reaction using both DBU (2 equiv) and cesium carbonate (0.5 equiv) was examined, maximum yield of **2a** was observed (Table 1, entry 7). However, the reaction using 1 equiv of DBU/0.5 equiv of cesium carbonate reduced the yield of **2a** to 69%. The reduced cesium carbonate resulted in decreasing the yield of **2a**. Specifically, the reactions with either DBU or cesium carbonate did not yield the desired products (Table 1, entries 12 and 13). We further investigated the reactions using various combinations of other solvents with H₂O. The results are shown in Table 1, entries 14–20. The reactions conducted in oxophilic solvents, such as THF, 1,4-dioxane, and methanol, yielded amide **2a**.

Nitromethane was proved to be effective for nitrile hydration. The suitable reaction conditions succeeded to scale-up the process for the preparation of 10 mmol of **2a** (Table 1, entry 7).

Using the above-mentioned optimized conditions, the scope of the present catalytic system, i.e., copper iodide/cesium carbonate/DBU in nitromethane–water, was explored for the hydration of various aromatic nitriles (Scheme 1). Benzonitrile and *p*-chlorobenzonitrile quantitatively isolated the corresponding amides **2b** and **2c**, accompanied by the aza-Henry products **3b** and **3c**. The hydration of *p*-methoxybenzonitrile, which generated the electron-donating substituent as a methoxy group, slightly decreased the yield of **2d**. In contrast, the nitrile **1d** was recovered. *o*-Substituents on the aromatic nitriles underwent hydration to produce amides **2e** and **2f** in 50–62% yields. Surprisingly, the reaction of methyl *p*-cyanobenzoate quantitatively converted into products without the hydrolysis of the intramolecular ester group to provide amide **2g** in 90% yield. This nitrile hydration was strongly influenced by the electronic effects

Table 1 Screening of Nitrile Hydration Using Copper Iodide/Cesium Carbonate/DBU in Nitromethane–Water

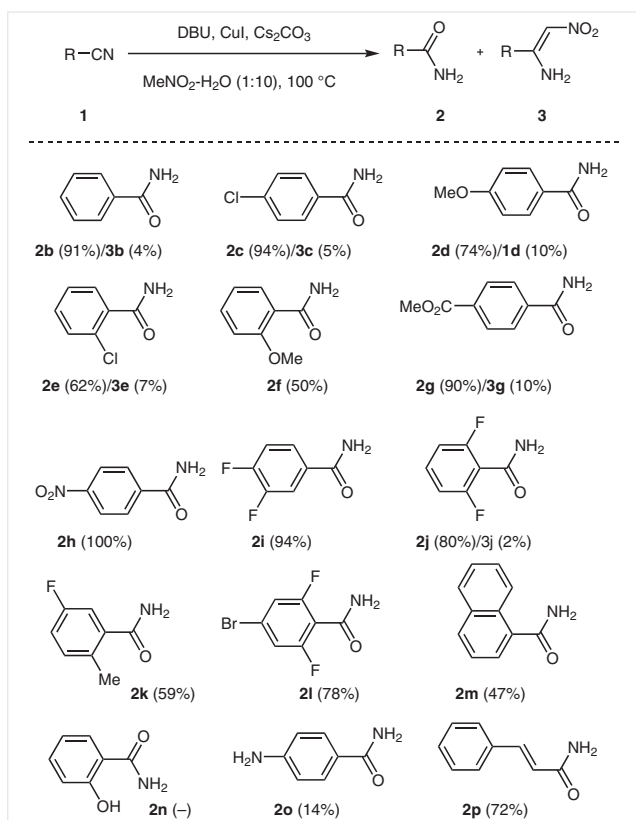
1a $\xrightarrow{\text{conditions}}$ 2a + 3a

Entry	CuI (equiv)	Base (equiv)	Solvent	Additives (equiv)	Temp (°C)/Time (h)	Yield of 1a (%)	Yield of 2a (%) ^a	Yield of 3a (%)
1	1	DBU (3)/Cs ₂ CO ₃ (1)/MS4Å	MeNO ₂ –HMPA (10:1)	–	85/0.75	–	10	87
2	1	DBU (3)/Cs ₂ CO ₃ (1)	MeNO ₂ –H ₂ O (1:10)	–	100/0.5	–	92	–
3	0.2	DBU (3)/Cs ₂ CO ₃ (1)	MeNO ₂ –H ₂ O (10:1)	Bu ₄ NHSO ₄ (0.2)	rt/0.25	10	23	–
4	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	MeNO ₂ –H ₂ O (10:1)	Bu ₄ NHSO ₄ (0.2)	85/2	–	43	–
5	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	MeNO ₂ –H ₂ O (1:1)	Bu ₄ NHSO ₄ (0.2)	100/1.5	–	87	2
6	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	H ₂ O	–	100/0.5	–	17	–
7	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	MeNO ₂ –H ₂ O (1:10)	–	100/0.5	–	92 ^b	6
8	0.2	DBU (1)/Cs ₂ CO ₃ (0.5)	MeNO ₂ –H ₂ O (1:10)	–	100/1	–	69	–
9	0.2	DBU (1)/Cs ₂ CO ₃ (0.2)	MeNO ₂ –H ₂ O (1:10)	–	100/7	–	40	–
10	0.1	DBU (2)/Cs ₂ CO ₃ (0.5)	MeNO ₂ –H ₂ O (1:10)	–	100/1.5	–	84	16
11	0.2	DBU (3)/Cs ₂ CO ₃ (0.5)	MeNO ₂ –H ₂ O (1:10)	–	100/3	–	66	–
12	0.2	DBU (3)	MeNO ₂ –H ₂ O (1:10)	–	100/4	–	trace	–
13	0.2	Cs ₂ CO ₃ (3)	MeNO ₂ –H ₂ O (1:10)	–	100/7	–	trace	–
14	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	ClCH ₂ CH ₂ Cl–H ₂ O (1:10)	–	100/0.5	–	trace	–
15	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	MeCN–H ₂ O (1:10)	–	100/8.5	–	35	–
16	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	DMF–H ₂ O (1:10)	–	100/3	17	12	–
17	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	THF–H ₂ O (1:10)	–	100/4.5	–	64	–
18	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	dioxane–H ₂ O (1:10)	–	100/10	–	81	–
19	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	toluene–H ₂ O (1:10)	–	100/4	23	20	–
20	0.2	DBU (2)/Cs ₂ CO ₃ (0.5)	MeOH–H ₂ O (1:10)	–	100/11	–	66	–

^aYields were calculated based on the isolated products after usual workup.

^bReaction was scaled to 10 mmol (70%).

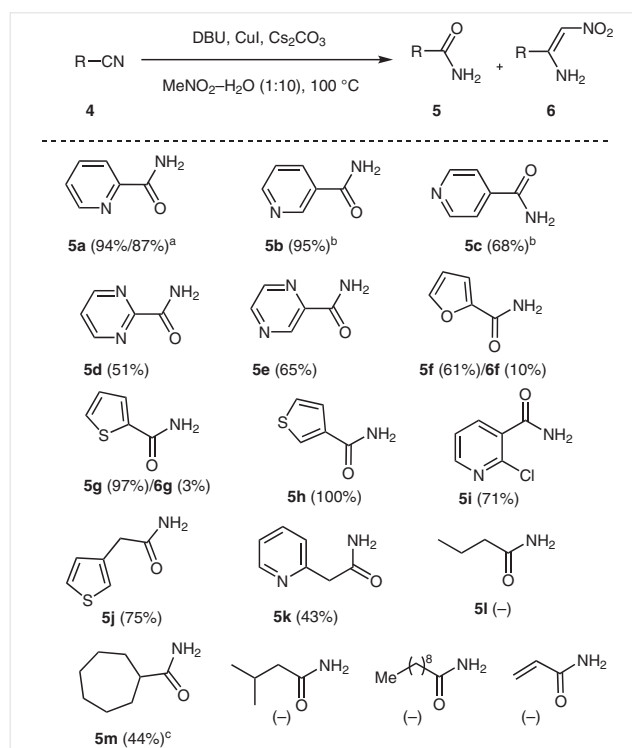
of the substituents on the aromatic ring of benzonitriles. *p*-Nitrobenzonitrile (**1h**) and 3,4-difluorobenzonitrile (**1i**) smoothly hydrated to quantitatively produce **2h** and **2i**. Interestingly, 2,6-difluorobenzonitrile that shows negligible influence of the substituent's position proceeded to afford **2j** without any differences in the reactivities of other benzonitriles. In contrast, *o*-methyl- and *p*-bromo-substituents of **1k** and **1l** did not tolerate the hydration and produced a relatively low yield. The bulky naphthonitrile produced a low yield of amide **2m**. The hydration of *o*-hydroxy **1n** and *p*-amino derivative **1o** did not proceed successfully. Neither the hydration of carbon-carbon double bond nor polymerization of cinnamonitrile (**1p**) occurred to afford a good yield of the amide **2p**.



Scheme 1 Substrate scope for nitrile hydration: substituted benzonitriles

Following the successful results obtained from benzonitriles, we focused on the catalytic hydration of heteroarenes (Scheme 2). The hydration of 2-cyanopyridine easily proceeded to exclusively yield 2-pyridinamide (**5a**). The reaction of 3-cyanopyridine (**4b**) was extremely slow; however, quantitatively produced nicotinamide (**5b**) in the preparation of 5 mmol scale of nicotinamide. In the nitrile hydration by CeO_2 in water, kinetic and DFT investigations supported the fact that the entropic barrier for the nitrile hydration of 2-cyanopyridine caused 10^7 -fold rate

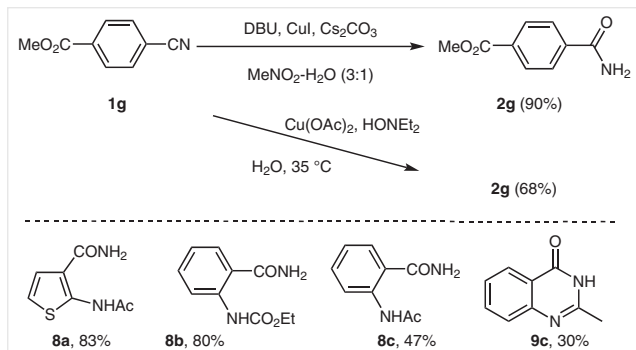
enhancement compared with that of 4-cyanopyridines (the heteroatom (N or O) affects the adjacent CN group).¹⁵ Fortunately, the hydration of 4-cyanopyridine (**4c**) by our protocol afforded the amide **5c** in satisfactory yield. While, the yields of both 2-pyrimidinocarboxamide (**5d**) and pyridinamide (**5e**), which have the important biological activities,² are moderate. Furan **5f** and thiophene-2-carboxamide (**5g**) were obtained using our protocol. In addition, the hydration of 3-thiophenecarbonitrile, 2-chloro-3-cyanopyridine, and other low reactive substrates, such as **5h** and **5i**, produced the corresponding amides. Fortunately, 2-heteroarylacetamides **5j** and **5k** were obtained in satisfactory yields. However, most aliphatic nitriles did not tolerate the nitrile hydration using the copper iodide/cesium carbonate/DBU in nitromethane system.



Scheme 2 Nitrile hydration of heteroaryl nitrile and others. ^a Reaction was scaled to 10 mmol. ^b Reaction was scaled to 5 mmol. ^c Reaction was scaled to 8 mmol.

Based on the impact of hydration of methyl *p*-cyanobenzoate observed in our protocol, we further investigated the functional compatibility of nitrile hydration using functionalized heteroaryl- and benzonitriles. First, we examined the hydration of methyl *p*-cyanobenzoate using another method comprising copper acetate/diethylhydroxyamine in water. A 60% yield of methyl 4-carbamoylbenzoate was obtained.¹⁶ Next, we selected the nitriles bearing sensitive functional groups for the hydrolysis and performed the nitrile hydration under our protocol. The hydration of *N*-(3-cyano-2-thienyl)acetamide (**7a**) under the optimal reaction

conditions afforded a high yield of 2-acetylamino-3-thiophenecarboxamide (**8a**, Scheme 3). The reaction of ethyl *N*-(2-cyanophenyl)carbamate also provided the corresponding amide **8b**. The reaction of *N*-(2-cyanophenyl)acetamide, however, provided 2-methyl-4(3*H*)-quinazoline (**9c**) in 30% yield, accompanied by the usual product, amide **8c**.

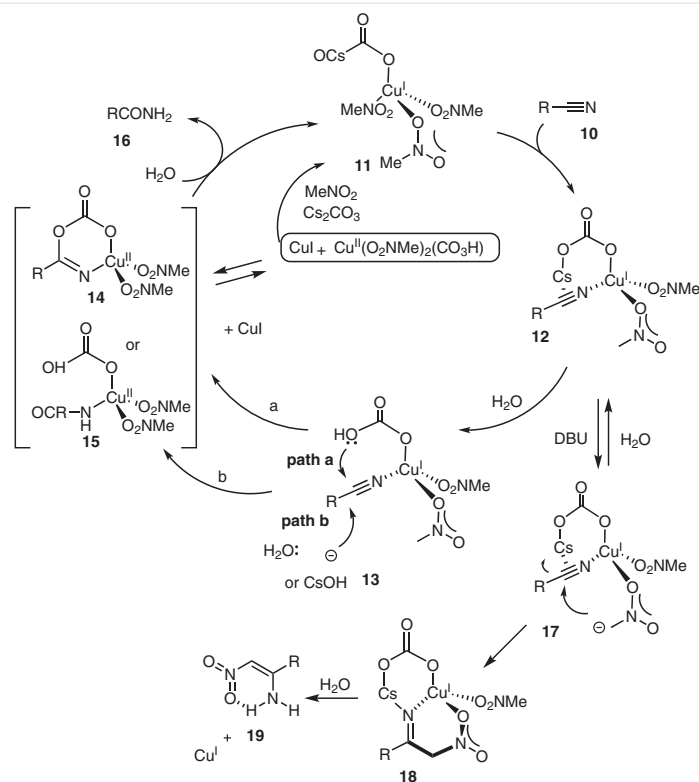


Scheme 3 Nitrile hydrations of functionalized benzo- and heteroaryl-nitriles

Finally, we proposed the nitrile hydration mechanism shown in Scheme 4. Based on our observations of the reaction medium and their NMR studies,¹⁴ the reactions would

proceed via the copper-coordinated intermediates and the catalytic hydration involves the copper(I)/copper(II) oxidation–reduction process. First, the hydration of nitrile **10** would proceed via the highly coordinated copper(I) catalyst **11**, which undergoes ligand exchange with nitrile to form **12**. Upon coordination to copper, the electron density of nitrile drastically decreases, thereby increasing nitrile's susceptibility to inter- or intramolecular attack by water or carboxylate (path a or b). Either **14** or **15** would yield amide **16**, whereas copper(I) is reformed by the copper(I) and copper(II)(*O*₂NMe)₂(CO₃H) complexes. High compatibility would be achieved via a stereoelectronic effect of the high-coordinated copper(I) catalyst.

In conclusion, the present study demonstrates facile nitrile hydration using copper iodide/cesium carbonate/DBU in nitromethane–water.¹⁷ The protocol tolerated various aryl-, heteroaryl, and heteroarylmethyl nitriles having high functional compatibility. We believe that the proposed method can be applied to other functionalized aryl- and heteroarylnitriles to directly yield the corresponding amides. Further studies using the highly coordinated copper catalysts are being conducted to investigate the intermolecular coupling reactions.



Scheme 4 Possible reaction pathway

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1609912>.

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- (17) **Typical Procedure for the Nitrile Hydration of Tolunitrile (1a)**
To a nitromethane (0.10 mL) solution of 4-methylbenzonitrile (**1a**, 30 mg, 0.256 mmol) were added H₂O (1.0 mL), DBU (78 mg, 0.512 mmol), copper(I) iodide (9.8 mg, 0.0512 mmol), and cesium(I) carbonate (42 mg, 0.128 mmol) at room temperature. The reaction mixture was heated at 100 °C for 1 h and then poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over MgSO₄. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with AcOEt–*n*-hexane (1:1) to give 4-methylbenzamide (**2a**, 32 mg, 92%) as pale yellow powders. ¹H NMR (400 MHz, CDCl₃): δ = 2.40 (3 H, s, CH₃), 6.10 (2 H, br s, NH), 7.25 (2 H, d, *J* = 8.2 Hz, ArH), 7.71 (2 H, d, *J* = 8.2 Hz, ArH).