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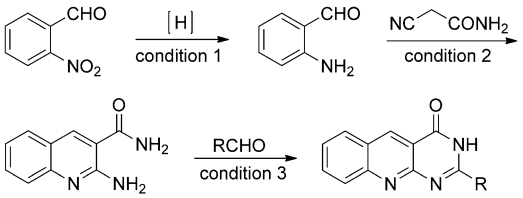
Multicomponent Reactions

Synthesis of 2-Aminoquinoline-3-carboamides and Pyrimido[4,5-*b*]quinolin-4-ones through Copper-Catalyzed One-pot Multicomponent Reactions

Xin-Ying Zhang,* Xiao-Jie Guo, and Xue-Sen Fan*[a]

Abstract: Pyrimido[4,5-*b*]quinolinones have attracted considerable interest from both chemical and medicinal scientists as these compounds display remarkable antimicrobial, anti-inflammatory, antitumor, antiallergy, analgesic, and antioxidant activities. The importance of pyrimido[4,5-*b*]quinolinones has stimulated enormous efforts to develop efficient methodologies for their synthesis. Herein, we disclose a novel synthetic protocol toward pyrimido[4,5-*b*]quinolin-4-ones through $Cu(OAc)_2$-catalyzed one-pot four-component reactions of 2-bromobenzaldehydes, aqueous ammonia, cyanoacetamides and aldehydes. The synthetic procedure combines amination/condensation/cyclization/dehydrogenation reactions in one pot, allowing synthesis of complex compounds in a simple and practical manner. Compared with literature procedures, the synthetic strategies developed herein showed advantages such as readily available and economically sustainable starting materials, structural diversity of products, good functional group tolerance, and a remarkably simple operation process.

Pyrimido[4,5-*b*]quinolinones are an important class of substances with potent antimicrobial,[1] anti-inflammatory,[1,2] antitumor,[3] antiallergy,[4] and analgesic activities.[1] So far, the pyrimido[4,5-*b*] quinolinone scaffold is usually constructed through condensation of 2-aminoquinoline-3-carboamides with carbonyl or carboxylate compounds.[1,3–8] While this synthetic strategy is reliable, the required 2-aminoquinoline-3-carboamides are commercially not available and are usually obtained via condensing cyanoacetamides with *o*-aminobenzaldehydes. Furthermore, *o*-aminobenzaldehydes are still of limited commercial availability or quite expensive and thus have to be prepared by reduction of *o*-nitrobenzaldehydes. As a result, up to three separate operations are involved in the preparation of pyrimido[4,5-*b*]quinolinones starting from cheap commercial reagents (Scheme 1).



Scheme 1. Currently used multistep preparation of pyrimido[4,5-*b*]quinolin-4-ones.

Compared with step-by-step transformations, one-pot multicomponent reactions (MCRs) usually enable the construction of complex molecules from simple and readily available starting materials and offer higher atom economy and better overall yields owing to the avoidance of separation and purification of the intermediates. As a result, MCRs have been used extensively in the construction of different chemical libraries.[9,10] In particular, copper-catalyzed MCRs with C–N bond formation as a key step are emerging as a highly efficient approach toward *N*-heterocyclic compounds.[11,12] In this regard, we have recently developed a one-pot four-component cascade reaction leading to pyrazolo[1,5-*c*]quinazolines and a one-pot three-component reaction affording quinolizines with copper-catalyzed amination of aryl halides as an initiating step by using aqueous ammonia as a cheap and convenient nitrogen source.[13] Encouraged by the above results, we proposed an alternative synthesis of pyrimido[4,5-*b*]quinolin-4-ones through copper-catalyzed one-pot four-component cascade reaction of the commercially available *o*-bromobenzaldehyde (**1**), aqueous ammonia (**2**), cyanoacetamide (**3**), and aldehyde (**4**) as shown in Scheme 2.

Initially, 2-bromobenzaldehyde (**1a**) was treated with aqueous ammonia (**2**), cyanoacetamide (**3a**), and benzaldehyde (**4a**) under the catalysis of CuI (0.1 equiv) in DMF. Unfortunately, this four-component reaction afforded a complicated mixture, and the expected 2-phenylpyrimido[4,5-*b*]quinolin-4(3*H*)-one (**5a**) was not obtained. Further attempts with regard to different catalysts and solvents did not give satisfying results as well. Considering that 2-aminoquinoline-3-carboamide (**6a**) serves as a key intermediate in the formation of **5a**, we went

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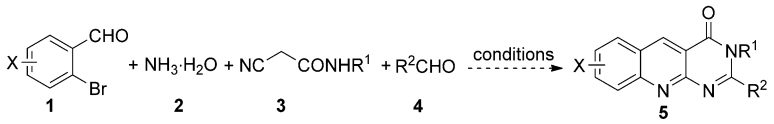
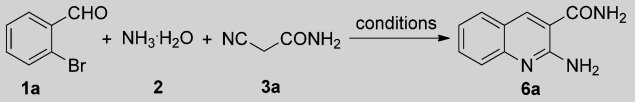


Scheme 2. Proposed one-pot four-component reaction leading to pyrimido[4,5-*b*]quinolin-4-ones.

one step back to check whether **6a** could be obtained from the reaction of **1a** with **2** and **3a**. Thus, **1a** was treated with **2** and **3a** in the presence of CuI (0.1 equiv) in DMF for 6 h. To our delight, it afforded **6a** in a yield of 41% (Table 1, entry 1). Encouraged by this preliminary result, thorough optimization

Table 1. Optimization for the formation of 2-aminoquinoline-3-carboamide (**6a**).[a]



Entry	Cu source	Solvent	Ligand	Base	*T* [°C]	Yield [%][b]
1	CuI	DMF	–	–	80	41
2	CuI	dioxane	–	–	80	37
3	CuI	*i*PrOH	–	–	80	33
4	CuI	DMSO	–	–	80	45
5	CuBr	DMSO	–	–	80	44
6	CuCl	DMSO	–	–	80	36
7	$CuCl_2$	DMSO	–	–	80	41
8	$Cu(OTf)_2$	DMSO	–	–	80	42
9	$Cu(OAc)_2$	DMSO	–	–	80	48
10	$Cu(OAc)_2$	DMSO	DMAP	–	80	41
11	$Cu(OAc)_2$	DMSO	L-Proline	–	80	46
12	$Cu(OAc)_2$	DMSO	1,10-phen	–	80	45
13	$Cu(OAc)_2$	DMSO	DMEDA	–	80	49
14	$Cu(OAc)_2$	DMSO	TMEDA	–	80	48
15	$Cu(OAc)_2$	DMSO	PivOH	–	80	43
16	$Cu(OAc)_2$	DMSO	–	Na_2CO_3	80	40
17	$Cu(OAc)_2$	DMSO	–	K_2CO_3	80	55
18	$Cu(OAc)_2$	DMSO	–	Cs_2CO_3	80	52
19	$Cu(OAc)_2$	DMSO	–	$K_3PO_4{\cdot}3H_2O$	80	44
20	**$Cu(OAc)_2$**	**DMSO**	**–**	**K_2CO_3**	**100**	**60**
21	$Cu(OAc)_2$	DMSO	–	K_2CO_3	110	57
22	$Cu(OAc)_2$[c]	DMSO	–	K_2CO_3	100	62
23	–	DMSO	–	K_2CO_3	100	–

[a] The reactions were run with 0.5 mmol of **1a**, 0.5 mmol of **3a**, 0.1 mmol of additive, 0.05 mmol of catalyst, 0.5 mmol of base, and 1 mL of 26% aqueous ammonia (**2**) in 2 mL of solvent in a sealed tube for 6 h. [b] Isolated yield. [c] 0.1 mmol of $Cu(OAc)_2$.

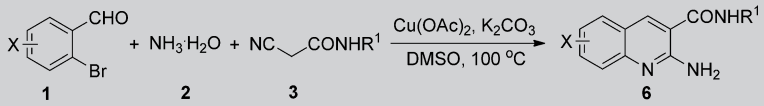
of the reaction conditions was then carried out. Firstly, 1,4-dioxane, *i*PrOH, or DMSO was tried as the reaction medium (Table 1, entries 2–4). Among them, DMSO gave a better yield of **6a** while *i*PrOH and 1,4-dioxane were less effective compared with DMF. Experiments with different copper salts showed that $Cu(OAc)_2$ was more effective than CuI, CuBr, CuCl, $CuCl_2$, or $Cu(OTf)_2$ for this reaction (Table 1, entries 4–9). In the next stage, the effect of several additives was also studied by using $Cu(OAc)_2$ as catalyst and DMSO as solvent. It was found that addition of 4-dimethylaminopyridine (DMAP), L-proline, 1,10-phenanthroline hydrate (1,10-phen), *N*,*N*′-dimethylethylene diamine (DMEDA), *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA), or 2,2-dimethylpropanoic acid (PivOH) did not improve the yield of **6a** (Table 1, entries 10–15). On the other hand, addition of K_2CO_3 or Cs_2CO_3 could increase the yield of **6a** (entries 17, 18) while Na_2CO_3 or $K_3PO_4{\cdot}3H_2O$ showed no obvious effect (entries 16, 19). Upon further screening, to our pleasure, we found that raising the reaction temperature from 80 °C to 100 °C could increase the yield of **6a** from 55% to 60% (Table 1, entries 17, 20). A temperature higher than 100 °C showed an adverse effect (entry 21). Furthermore, it was observed that raising the amount of $Cu(OAc)_2$ from 0.1 equiv to 0.2 equiv did not improve the reaction obviously (Table 1, entry 22). On the other hand, no formation of **6a** was observed without a copper catalyst (Table 1, entry 23). In summary, treating **1a**, **2**, and **3a** with 0.1 equiv of $Cu(OAc)_2$ and 1 equiv of K_2CO_3 in DMSO at 100 °C for 6 h afforded **6a** in a yield of 60%.

With the optimized reaction conditions in hand, the scope and generality of this cascade reaction leading to 2-aminoquinoline-3-carboamides (**6**) were explored. Firstly, several 2-bromobenzaldehydes (**1**) bearing different substituents were studied as possible substrates to react with **2** and **3a**. The results listed in Table 2 showed that they underwent this cascade reaction successfully and produced the desired 2-aminoquinoline-3-carboamides in yields ranging from 48% to 60% (Table 2, entries 1–8). Various functional groups, such as fluoro, chloro, trifluoromethyl, methyl, and methoxyl were well tolerated under the reaction conditions. Then, some *N*-substituted cyanoacetamides (**3**) were also tested. We were pleased to find that propyl-, benzyl-, phenethyl-, and cyclopropyl-substituted cyanoacetamides reacted with different 2-bromobenzaldehydes and aqueous ammonia smoothly to give *N*-substituted 2-aminoquinoline-3-carboamides in moderate yields (Table 2, entries 9–16).

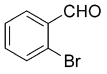
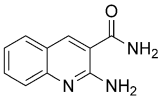
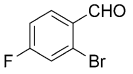
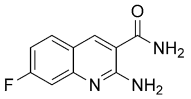
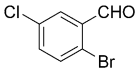
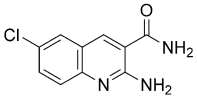
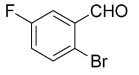
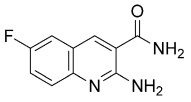
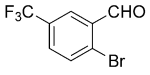
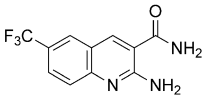
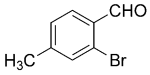
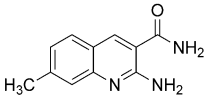
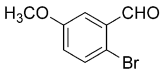
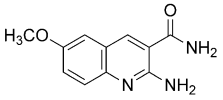
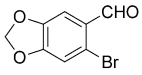
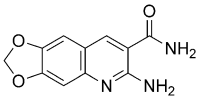
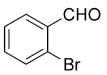
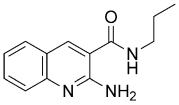
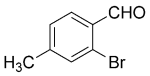
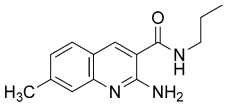
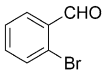
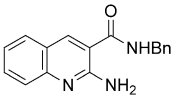
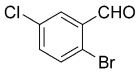
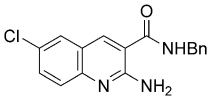
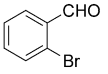
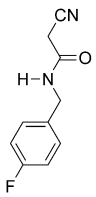
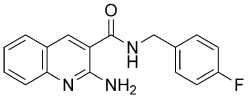
Having confirmed that 2-aminoquinoline-3-carboamides (**6**) could be smoothly formed via the reaction of **1**, **2**, and **3**, we proceeded to try our proposed synthesis of pyrimido[4,5-*b*]quinolinone as shown in Scheme 2 again, yet following an alternative operational method. Thus, instead of treating the mixture of **1a**, **2**, **3a**, and **4a** with copper catalyst, **1a**, **2**, and **3a** were firstly treated with $Cu(OAc)_2$ and K_2CO_3 in DMSO at 100 °C for 6 h, and then benzaldehye (**4a**) was added. The resulting mixture was stirred at 100 °C under air for 2 h. Subsequent workup of the reaction gave the desired pyrimido[4,5-*b*]quinolin-4(3*H*)-one (**5a**) in a yield of 46% (Scheme 3).

Encouraged by this promising result, the generality for the synthesis of **5** was studied with different 2-bromoaldehydes (**1**), cyanoacetamides (**3**), and aldehydes (**4**). The results listed in Table 3 showed some notable features: 1) 2-bromobenzaldehydes of various substitution patterns took part in this cascade process smoothly and produced a series of pyrimido[4,5-*b*]quinolin-4(3*H*)-ones (**5**) in reasonably good yields; 2) in addition to cyano-acetamide (**3a**), its *N*-substituted analogues were also suitable for this reaction; 3) aryl aldehydes (**4**) with either elec-

Table 2. Synthesis of 2-aminoquinoline-3-carboamides (**6**).[a]



1 2 3 6

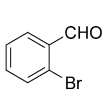
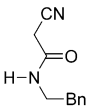
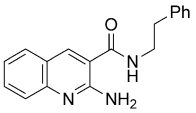
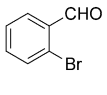
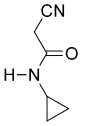
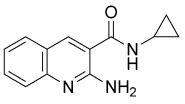
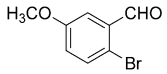
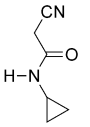
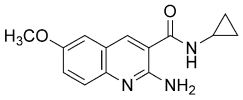
Entry	1	3	Product (6)		Yield [%][b]
1				**6a**	60
2				**6b**	57
3				**6c**	53
4				**6d**	54
5				**6e**	50
6				**6f**	56
7				**6g**	52
8				**6h**	48
9				**6i**	61
10				**6j**	60
11				**6k**	48
12				**6l**	43
13				**6m**	41

tron-donating or electron-withdrawing group reacted smoothly with the in situ-formed 2-aminoquinoline-3-carboamides to give **5**; 4) no obvious steric effect was observed with *ortho*-substituted aryl aldehydes; and 5) in addition to aryl aldehydes, butyraldehyde was also compatible to give **5n** in 44% yield.

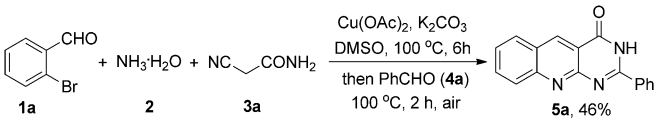
To elucidate the reaction mechanism, some control experiments were carried out (Scheme 4). Firstly, **6a** was treated with **4a** in DMSO at 100 °C for 6 h in the absence of $Cu(OAc)_2$ and K_2CO_3. From this reaction, 2-phenyl-2,3-dihydropyrimido-[4,5-*b*]quinolin-4(1*H*)-one (**7**) was obtained in a yield of 36% along with trace amount of **5a**. In the presence of 0.1 equiv of $Cu(OAc)_2$, on the other hand, **5a** and **7** were formed in 30% and 21% yield, respectively. With 1 equiv of K_2CO_3, the starting materials were consumed in 2 h, and **7** was obtained in a yield of 80%. Notably, in the presence of 0.1 equiv of $Cu(OAc)_2$ and 1 equiv of K_2CO_3, **5a** was formed in a yield of 85%. When the reaction was carried out under nitrogen instead of air atmosphere, it mainly afforded **7**. These observations (Scheme 4) together with the results listed in Table 1 suggested that: 1) $Cu(OAc)_2$ was not only indispensable for the C–N coupling between **1** and **2** but also crucial for the oxidative aromatization of the in situ-formed **7** to afford **5a**; 2) K_2CO_3 acted as an effective promoter in both the formation of **6a** and the cyclization of the in situ-formed **6a** with **4a** to give **7**; 3) air was the stoichiometric oxidant for the oxidative aromatization of **7** toward **5a**.

Based on the above facts, a plausible pathway for the formation of **5a**, **6a**, and **7** is proposed in Scheme 5. Firstly, copper-catalyzed amination of

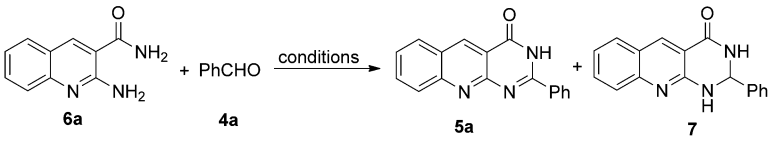
Table 2. (Continued)

Entry	1	3	Product (6)		Yield [%][b]
14				**6n**	56
15				**6o**	50
16				**6p**	51

[a] The reactions were run with 0.5 mmol of **1**, 0.5 mmol of **3**, 0.05 mmol of $Cu(OAc)_2$, 0.5 mmol of K_2CO_3, and 1 mL of 26% aqueous ammonia (**2**) in 2 mL of DMSO in a sealed tube at 100 °C for 6 h. [b] Isolated yield.

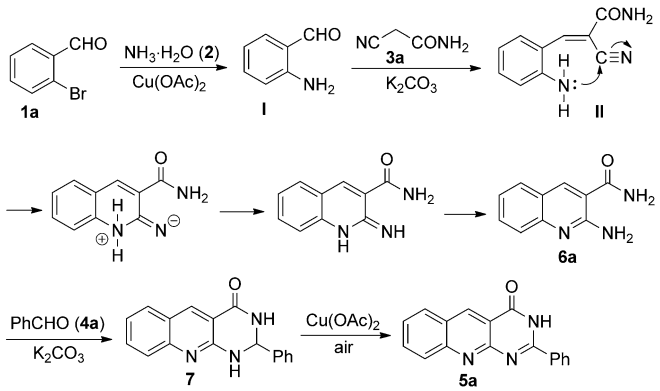


Scheme 3. Formation of **5a** from a sequential one-pot reaction of **1a**, **2**, **3a**, and **4a**.



	5a	7
I: 100 °C, 6 h, air	trace	36%
II: 0.1 eq. of $Cu(OAc)_2$, 100 °C, 6 h, air	30%	21%
III: 1 eq. of K_2CO_3, 100 °C, 2 h, air	trace	80%
IV: 0.1 eq. of $Cu(OAc)_2$, 1 eq. of K_2CO_3, 100 °C, 2 h, air	85%	trace
V: 0.1 eq. of $Cu(OAc)_2$, 1 eq. of K_2CO_3, 100 °C, 2 h, N_2	20%	60%

Scheme 4. Reactions of **6a** with **4a** under different reaction conditions.



Scheme 5. Plausible mechanism for the formation of **5a**, **6a**, and **7**.

2-bromoaldehyde (**1a**) with ammonia (**2**) affords 2-aminobenzaldehyde (**I**). Base-promoted condensation of **I** with cyanoacetamide (**3a**) leads to 3-(2-aminophenyl)-2-cyanoacrylamide (**II**). Subsequent intramolecular cyclization of **II** gives 2-aminoquinoline-3-carboamide (**6a**). In the next stage, base-promoted condensation of **6a** with benzaldehyde (**4a**) affords **7**. Catalyzed by $Cu(OAc)_2$ and promoted by air, **7** then undergoes an oxidative dehydrogenation to afford **5a**.

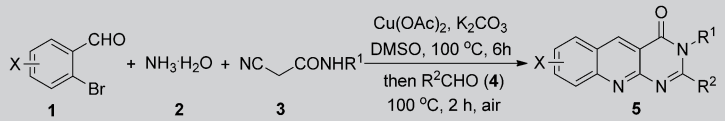
In summary, we have developed a convenient and economical synthesis of 2-aminoquinoline-3-carboamides and pyrimido[4,5-*b*]quinolin-4(3*H*)-ones via copper-catalyzed, base-promoted one-pot multicomponent cascade reactions using cheap commercial starting materials. It is particularly noteworthy that the synthetic procedure toward pyrimido[4,5-*b*]quinolin-4(3*H*)-ones combines amination/condensation/cyclization/dehydrogenation reactions in one pot, allowing synthesis of complex compounds in a simple and practical manner. Preliminary studies with regard to the reaction mechanism revealed that the successful combination of these single transformations in one pot is largely due to the multi functions of the copper catalyst as well as the dual role of the base promoter. Compared with literature procedures for the synthesis of the title compounds, the synthetic strategies developed herein showed advantages such as readily available and economically sustainable starting materials, structural diversity of products, good functional group tolerance, and a remarkably simple operation process.

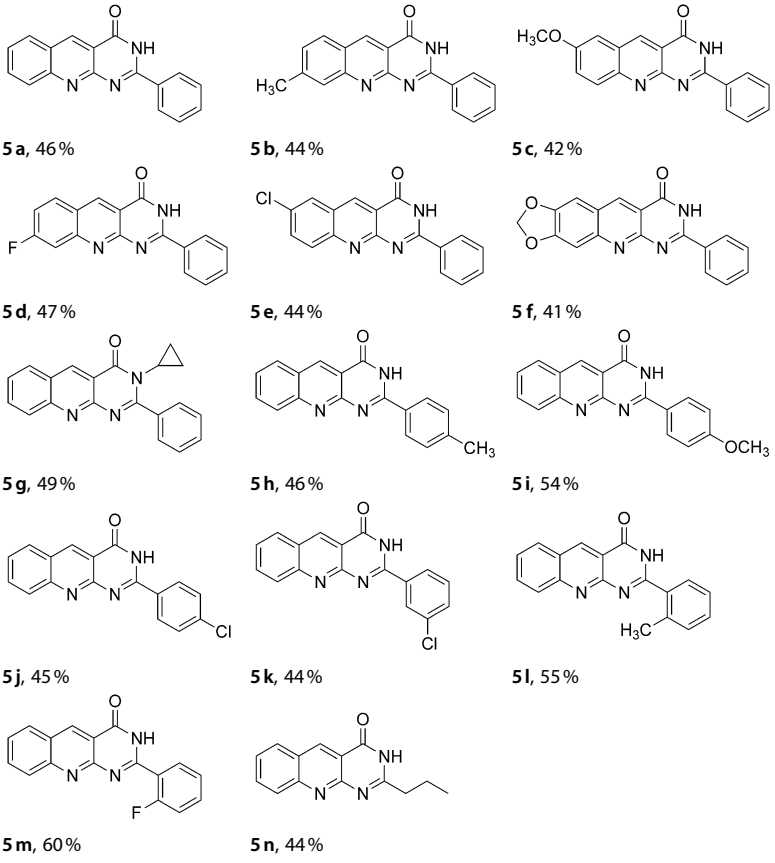
Experimental Section

General procedure for the preparation of 2-aminoquinoline-3-carboamides (6)

To a tube containing a solution of 2-bromobenzaldehyde **1** (0.5 mmol) and cyanoacetamide **3** (0.5 mmol) in DMSO (2 mL) were added $Cu(OAc)_2$ (0.05 mmol), K_2CO_3 (0.5 mmol), and aqueous ammonia (26%, 1 mL). Then, the tube was sealed, and the mixture was stirred at 100 °C for 6 h. After being cooled to room temperature, the reaction mixture was added to saturated brine (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic

Table 3. Synthesis of pyrimido[4,5-*b*]quinolin-4(3*H*)-one (**5**).[a,b]





[a] The reactions were run with 0.5 mmol of **1**, 0.5 mmol of **3**, 0.05 mmol of $Cu(OAc)_2$, 0.5 mmol of K_2CO_3, and 1 mL of 26% aqueous ammonia (**2**) in 2 mL of DMSO in a sealed tube at 100 °C for 6 h, and then treated with 0.75 mmol of **4** at 100 °C under air for 2 h. [b] Isolated yield.

layer was washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:2) to afford 2-aminoquinoline-3-carboamide derivative **6**.

General procedure for the preparation of pyrimido[4,5-b]quinolin-4-ones (5)

To a tube containing a solution of 2-bromobenzaldehyde **1** (0.5 mmol) and cyanoacetamide **3** (0.5 mmol) in DMSO (2 mL) were added $Cu(OAc)_2$ (0.05 mmol), K_2CO_3 (0.5 mmol) and aqueous ammonia (26%, 1 mL). Then, the tube was sealed, and the mixture was stirred at 100 °C for 6 h. After being cooled to room temperature, the tube was opened, and aldehyde **4** (0.75 mmol) was added. After being stirred at 100 °C for 2 h, the reaction mixture was added to saturated brine (10 mL) and extracted with ethyl acetate(10 mL×3). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to afford pyrimido[4,5-*b*]quinolin-4-one derivative **5**.

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Keywords: 2-aminoquinoline-3-carboamides · copper catalysis · multicomponent reactions · one-pot reactions · pyrimido-[4,5-*b*]quinolin-4-ones

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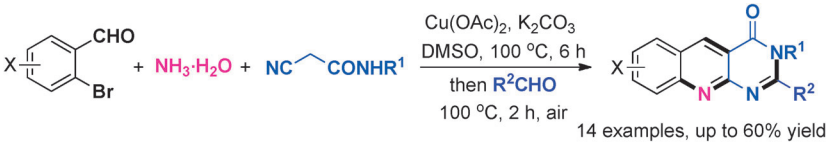

You have to be practical: Practical syntheses of 2-aminoquinoline-3-carboamides and pyrimido[4,5-*b*]quinolin-4-ones via $Cu(OAc)_2$-catalyzed and K_2CO_3-promoted one-pot multicomponent reactions of 2-bromobenzaldehydes with cyanoacetamides and aqueous ammonia/aldehydes were developed.

Multicomponent Reactions

X.-Y. Zhang, X.-J. Guo, X.-S. Fan**

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Synthesis of 2-Aminoquinoline-3-carboamides and Pyrimido[4,5-*b*]quinolin-4-ones through Copper-Catalyzed One-pot Multicomponent Reactions