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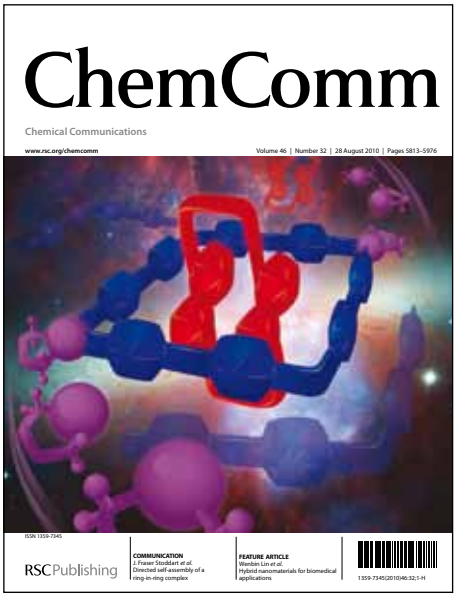

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ARTICLE TYPE

Auto-tandem catalysis: synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones via copper-catalyzed aza-Michael addition–aerobic dehydrogenation–intramolecular amidation

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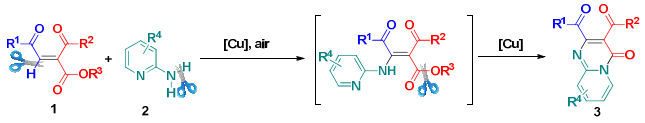
A copper-catalyzed synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones has been developed from 1,4-enediones and 2-aminoheterocycles with air as the oxidant. Copper catalyst in this reaction could promote three mechanistically distinct transformations of aza-Michael addition, aerobic dehydrogenation and intramolecular amidation.

Nitrogen-containing heterocycles are ubiquitous in natural products and pharmaceutical drugs,[1] therefore, considerable attention has been paid to their efficient synthetic methods.[2] Recently, an increasing number of *N*-heterocycles have been prepared by copper-catalyzed aerobic oxidative C–N formation strategy, which has incomparable advantages in atom economy, bond forming efficiency and environmental benignity.[3] Meanwhile, auto-tandem catalysis involving two or more mechanistically different transformations promoted by a single catalyst has attracted much interests of chemists, which could greatly improve the catalyst utilization efficiency.[4] Inspired by these excellent synthetic strategies, we suppose that it would be a highly efficient method for synthesis of *N*-heterocycles by incorporating the copper-catalyzed aerobic oxidative C–N formation into auto-tandem catalysis reactions.

The 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton is a privileged scaffold in medicinal chemistry, which has shown broad biological activities, such as antipsychotic, antiallergic, antidepressant, the tranquillizing agent, antihypertensive and antiulcerative.[5] However, only limited methods are available for their synthesis, which usually need waste-producing leaving groups (–NR, –OR, $–SCH_3$, $–SOCH_3$,–Cl, –Br, –I) and suffer from high temperature, strong acids or bases.[6] Herein, we would like to report a highly efficient method for synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones from 1,4-enediones and 2-aminopyridines by copper-promoted auto-tandem catalysis strategy (Scheme 1).



Scheme 1 Proposed reaction route

Initially, 1,4-enedione **1a** and 2-aminopyridine **2a** were chosen as model substrates to optimize the reaction conditions. Fortunately, the desired product **3aa** was obtained in 58% yield when the reaction was conducted in DMF with 0.05 equiv of $Cu(OAc)_2·H_2O$ as catalyst under air at 80 °C (Table 1, entry 1). Much to our satisfaction, by increasing the catalyst loading to 0.2 equiv, product **3aa** was obtained in 87% yield (entry 3). When the reaction was conducted in absence of copper catalyst, no desired product was obtained (entry 4). When the reaction was conducted under nitrogen, only 9% yield was obtained (entry 5). These results indicated that copper catalyst and air are necessary for this reaction. When the reaction was conducted at lower or higher temperature (60 or 100 °C), decreased yields were obtained (entries 6–7). Other copper catalysts and solvents were then screened under air at 80 °C, but no better results were obtained (entries 8–20).

With this optimized result in hand, we next explored the scope of this reaction. Based on our previously reported cross-coupling reaction of 1,3-dicarbonyl compounds and methyl ketones,[7] a series of diversely substituted 1,4-enediones **1** were prepared. As shown in Table 2, we first examined the scope of this reaction for R^1 substituents. For example, substrates with electron-neutral (–H, –Me), electron-donating(–OMe), electron-withdrawing ($–NO_2$) and sterically hindered (1-naphthyl, 2-naphthyl) R^1 substituents could be smoothly transformed into their corresponding products in good to high yields (Table 2, entries 1–6; 71–88%). To our delight, moderate to high yields were obtained with halogenated and hydroxylated R^1 substituents (entries 7–10; 52–86%). The heteroaryl groups for R^1 were also investigated, such as 2-furyl, 2-benzofuryl and 3-thienyl groups, their corresponding products were also obtained in high yields (entries 11–13; 83–89%). Much to our satisfaction, when R^1 was unsaturated (*E*)-Ph-(CH=CH)- group, its corresponding

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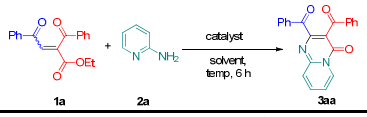
Table 1. Optimization of the Reaction Condition[a]



Entry	Catalyst (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	$Cu(OAc)_2·H_2O$ (0.05)	DMF	80	58
2	$Cu(OAc)_2·H_2O$ (0.1)	DMF	80	72
3	$Cu(OAc)_2·H_2O$ (0.2)	DMF	80	87
4	—	DMF	80	—[d]
5[c]	$Cu(OAc)_2·H_2O$ (0.2)	DMF	80	9
6	$Cu(OAc)_2·H_2O$ (0.2)	DMF	60	78
7	$Cu(OAc)_2·H_2O$ (0.2)	DMF	100	82
8	$CuBr_2$ (0.2)	DMF	80	54
9	$CuCl_2$ (0.2)	DMF	80	48
10	$CuSO_4$ (0.2)	DMF	80	83
11	CuO (0.2)	DMF	80	46
12	CuBr (0.2)	DMF	80	74
13	CuCl (0.2)	DMF	80	72
14	Cu_2O (0.2)	DMF	80	70
15	CuI (0.2)	DMF	80	82
16	$Cu(OAc)_2·H_2O$ (0.2)	DMSO	80	79
17	$Cu(OAc)_2·H_2O$ (0.2)	CH_3CN	80	60
18	$Cu(OAc)_2·H_2O$ (0.2)	C_2H_5OH	78	56
19	$Cu(OAc)_2·H_2O$ (0.2)	CH_3NO_2	80	72
20	$Cu(OAc)_2·H_2O$ (0.2)	1,4-dioxane	80	66

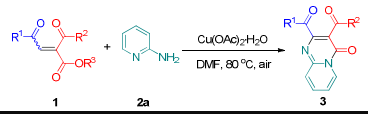
[a] Unless otherwise specified, all reaction were carried out using **1a** (0.5 mmol, 1.0 equiv), **2a** (0.55 mmol, 1.1 equiv) and catalysts (0.2 equiv) in 2.5 mL solvent under air for 6 h. [b] Isolated yields. [c] Under N_2. [d] No desired products were obtained.

product was obtained in good yield (entry 14; 74%). As to the substituents R^2, various electrondonating (–OMe), electron-withdrawing ($–NO_2$), and halogenated substituents (–Cl, –F) were compatible with the reaction condition, and their corresponding products were obtained in high yields (entries 15–18; 75–81%).[8] To our delight, when R^2 was 2-furyl group or methyl group, the reaction proceeded cleanly to give the desired products with excellent yields (entries 19–20; 87–91%).

We next examined the scope of this reaction for 2-aminopyridines **2** (Table 3). When they were substituted with methyl group at 3-, 4- or 5- positions, the corresponding products were obtained in good to high yields (74–85%; **3ab**–**3ad**). To our delight, halogen-substituted 2-aminopyridines (5-Cl, 5-Br) could also afford the desired products in good yields (58–64%; **3ae**–**3af**). Gratifyingly, when 2-aminobenzothiazole was used as substrate, the reaction performed very well and the corresponding product **3ag** was obtained in good yield (71%; **3ag**).

To provide insight into the reaction mechanism, a control experiment was performed (Scheme 2). When 2-amino-6-methylpyridine **2h** was used as substrate, only the C–N coupling product **4ah** was obtained with 68% yield, which may be due to the steric hindrance of 6-methyl group (Scheme 2a). In contrary, when the reaction was conducted in absence of copper catalyst, no desired product **4ah** was obtained (Scheme 2b). These results clearly confirmed that $Cu(OAc)_2·H_2O$ could efficiently catalyze the intermolecular C–N bond formation via aza-Michael addition–aerobic dehydrogenation. To further verify copper catalyst was necessary for the intramolecular cyclization via amide bond formation, we first obtained the C–N coupling

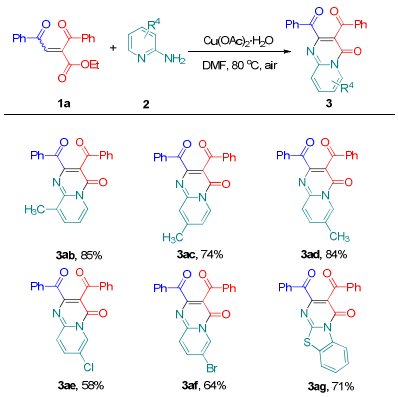
Table 2. Scope of unsymmetrical 1,4-enediones **1**[a]



Entry	1	R^1	R^2	R^3	3	Yield (%)[b]
1	**1a**	Ph	Ph	Et	**3aa**	87
2	**1b**	4-Me-Ph	Ph	Et	**3ba**	88
3	**1c**	4-OMe-Ph	Ph	Et	**3ca**	82
4	**1d**	4-NO_2-Ph	Ph	Et	**3da**	71
5	**1e**	1-naphthyl	Ph	Et	**3ea**	80
6	**1f**	2-naphthyl	Ph	Et	**3fa**	82
7	**1g**	4-Cl-Ph	Ph	Et	**3ga**	85
8	**1h**	4-Br-Ph	Ph	Et	**3ha**	86
9	**1i**	4-F-Ph	Ph	Et	**3ia**	84
10	**1j**	4-OH-Ph	Ph	Et	**3ja**	52
11	**1k**	2-furyl	Ph	Et	**3ka**	89
12	**1l**	2-benzofuryl	Ph	Et	**3la**	88
13	**1m**	3-thienyl	Ph	Et	**3ma**	83
14	**1n**	(*E*)-Ph-(CH=CH)-	Ph	Et	**3na**	74
15	**1o**	Ph	4-OMe-Ph	Et	**3oa**	79
16	**1p**	Ph	4-NO_2-Ph	Et	**3pa**	75
17	**1q**	Ph	4-Cl-Ph	Me	**3qa**	81
18	**1r**	Ph	4-F-Ph	Me	**3ra**	78
19	**1s**	Ph	2-furyl	Et	**3sa**	87
20	**1t**	Ph	CH_3	Et	**3ta**	91

[a] Reaction was carried out using **1** (1.0 mmol, 1.0 equiv), **2a** (1.1 mmol, 1.1 equiv) and $Cu(OAc)_2·H_2O$ (0.2 mmol, 0.2 equiv) in 5 mL DMF at 80 °C under air. [b] Isolated yields.

Table 3. Scope of 2-aminoheterocycles **2**[a]

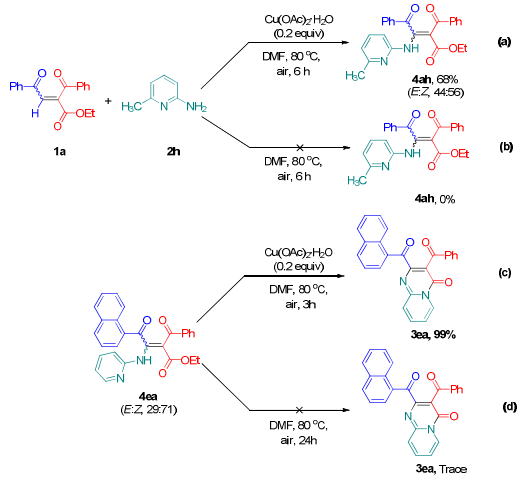


[a] Reaction was carried out using **1a** (1.0 mmol, 1.0 equiv), **2** (1.1 mmol, 1.1 equiv) and $Cu(OAc)_2·H_2O$ (0.2 mmol, 0.2 equiv) in 5 mL DMF at 80 °C under air. [b] Isolated yield.

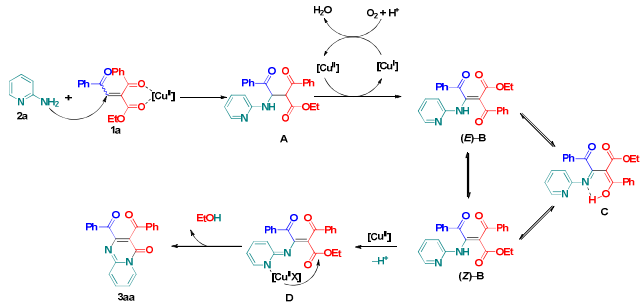
intermediate **4ea** in 17% yield when 1,4-enedione **1e** was treated with 2-aminopyridine **2a** in presence of 0.05 equiv of $Cu(OAc)_2·H_2O$ under air for 2 h.[8] When **4ea** was used as substrate, a quantitative yield of **3ea** was obtained with 0.2 equiv of $Cu(OAc)_2·H_2O$ as catalyst for 3 h (Scheme 2c). In contrary, only trace of **3ea** was obtained in absense of $Cu(OAc)_2·H_2O$ (Scheme 2d). These results clearly confirmed that $Cu(OAc)_2·H_2O$ could efficiently catalyze the intramolecular cyclization via amide bond formation.

Based on the previous studies, a possible reaction mechanism was proposed in scheme 3 with **1a** and **2a** as an example. The aza-Michael addition of **1a** with **2a** under Cu(II) catalysis would first generate intermediate **A**, which then

undergoes copper-catalyzed aerobic dehydrogenation reaction to generate *E*/*Z* isomers of intermediate **B**.[9] The *E*-isomer of intermediate **B** could undergo isomerization reaction to generate its *Z*-isomer through intermediate **C,** and finally it could afford the product **3aa** through copper catalyzed intramolecular amide bond formation. Because the reaction was conducted under air atmosphere, the formed Cu(I) species in this reaction could be oxidized by air to Cu(II), so that the reaction can be catalytic in Cu with air as terminal oxidant. It's noteworthy that $Cu(OAc)_2 \cdot H_2O$ played two critical roles in this reaction, which could not only catalyze the intermolecular C–N bond formation through aza-Michaial addition/aerobic dehydrogenation, but also catalyze the subsequent intramolecular cyclization via amide bond formation.

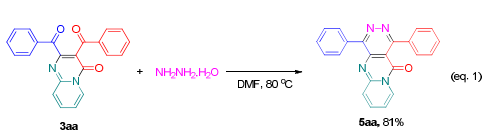


Scheme 2. Control experiments



Scheme 3. Proposed reaction mechanism

Considering the γ-diketone functional group in products could easily undergo further transformation, we treated **3aa** with hydrazine hydrate in DMF, and a novel fused heterocycle **5aa** was readily prepared in 81% yield (eq. 1). It's noteworthy that this novel fused heterocycle scaffold of **5aa** has never been reported before.



In conclusion, we have developed a novel copper catalyzed synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones from 1,4-enediones and 2-aminoheterocycles with air as the oxidant. It's noteworthy that copper catalyst in this reaction could promote three mechanistically distinct transformations of aza-Michael addition, aerobic dehydrogenation and intramolecular amidation. Wide substrate scope, mild reaction condition, and air as oxidant are also significant advantages of this reaction. Further application of this method is underway in our laboratory.

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Auto-tandem catalysis: synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones via copper-catalyzed aza-Michael addition–aerobic dehydrogenation–intramolecular amidation

A copper-catalyzed synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones has been developed from 1,4-enediones and 2-aminoheterocycles with air as the oxidant. The copper catalyst in this reaction could promote three mechanistically distinct transformations of aza-Michael addition, aerobic dehydrogenation and intramolecular amidation.