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Intramolecular redox cyclization reaction access to cinnolines from 2-nitrobenzyl alcohol and benzylamine via intermediate 2nitrosobenzaldehyde†

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A transition-metal-free intramolecular redox cyclization reaction for the synthesis of cinnolines has been developed from 2-nitrobenzyl alcohol and benzylamine. Mechanistic investigations disclosed the involvement of a key intramolecular redox reaction, followed by condensation, azo isomerization to hydrazone, cyclization, and aromatization to form the desired products. Notably, the formation of intermediate 2-nitrosobenzaldehyde and (E)-2-(2-benzylidenehydrazineyl) benzaldehyde plays an important role in this transformation.

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Cinnolines are important nitrogen-containing heterocyclic organic compounds which have attracted widespread attention in the field of organic, materials and pharmaceutical chemistry. They are known to display interesting biological activities such as inhibitory activity toward CSF-1R,2 antitumor,3 antiviral,4 anti-inflammatory5 and sedative effects6 (Fig. 1).

The classical synthetic approaches to cinnolines start from N-phenylhydrazones or N-phenylazo compounds via Rhcatalyzed C-H activation,7 Pd-catalyzed annulation,8 or Cucatalyzed C-H functionalization/cyclization strategies.9 For example, in 2012, Ge's group reported a Cu-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of Nmethyl-N-phenylhydrazones for the formation of cinnolines (Scheme 1a). 10 Subsequently, Lin and coworkers described a Rhcatalyzed redox-neutral annulation of azo and diazo compounds through a tandem C-H activation and C-N bond formation strategy (Scheme 1b).11 More recently, Xu et al. developed a copper-catalyzed aerobic annulation involving a dehydrogenative amination to afford cinnolines (Scheme 1c).12 Interestingly, Wang's group reported a Cu-catalyzed cascade cyclization to achieve regioselective synthesis of functionalized cinnolines (Scheme 1d).13 Although great achievements have been made,14 the development of a novel transitionmetal-free mediated reaction from simple substrates to obtain the cinnoline framework is highly desirable. For example, in

2016, Wang and coworkers developed a one-pot cascade reaction for the construction of 4-amido-cinnoline derivatives (Scheme 1e).15 In our previous works, we developed a novel transition-metal-free multicomponent coupling cyclization reaction for synthesis of cinnoline derivatives.16 Inspired by these works, herein, we reported a transition-metal-free intramolecular redox cyclization reaction for straightforward access to cinnolines from 2-nitrobenzyl alcohol and benzylamine

Initially, the reaction was investigated using 2-nitrobenzyl alcohol (1a) and benzylamine (2a) as model substrates (Table 1). The desired product, 3-phenylcinnoline (3aa), was furnished with 15% yield when the reaction proceeded in the presence of 20.0 equiv. of KOH at 100 °C for 3 h in i PrOH (entry 1). At the same time, 2-phenylquinazoline (4) was also obtained in 12% yield. Unfortunately, the target product 3aa was not obtained when the reaction proceeded in H₂O (entry 2). Intriguingly, the yield of 3-phenylcinnoline (3aa) was increased to 36% when the

Fig. 1 Bioactive cinnoline derivatives.

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(a) Ge's work: Cu-catalyzed aerobic dehydrogenative cyclization

$$\begin{array}{c} R^2 \\ R^1 \\ \hline \\ R^1 \\ \hline \\ R^2 \\ \hline \\ N \\ N \\ \end{array} \begin{array}{c} CuSO_4, Cul \\ pyridine, CF_3SO_3H \\ \hline \\ O_2, DMF, 110 °C \\ \end{array} \begin{array}{c} R^1 \\ \hline \\ N \\ \end{array} \begin{array}{c} R^2 \\ \hline \\ N \\ \end{array}$$

(b) Lin's work: Rh-catalyzed redox-neutral annulation

$$R^{1} \underbrace{\hspace{1cm} \stackrel{\mathsf{N} \longrightarrow \mathsf{N}}{\mathsf{N}^{\mathsf{Boc}}}}_{\mathsf{H}} + \underbrace{\hspace{1cm} \stackrel{\mathsf{O}}{\mathsf{R}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{CO}_{\mathsf{2}}\mathsf{R}^{\mathsf{3}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} [\mathsf{RhCp^{*}Cl_{\mathsf{2}}}]_{\mathsf{2}}/\mathsf{AgSbF}_{\mathsf{6}}}_{\mathsf{PivOH/DCE}, 50~°C} \underbrace{\hspace{1cm} \mathsf{R}^{\mathsf{1}} \underbrace{\hspace{1cm} \mathsf{CO}_{\mathsf{2}}\mathsf{R}^{\mathsf{3}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{CO}_{\mathsf{2}}^{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{CO}_{\mathsf{2}}^{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}} \underbrace{\hspace{1cm} \mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}}_{\mathsf{N}^{\mathsf{2}}$$

(c) Xu's work: Cu-catalyzed aerobic annulation

(d) Wang's work: Cu-catalyzed cyclization

X=F, OCH_3 , $N(CH_3)_2$

(e) Wang's work: BF3-ehterate-promoted cascade reaction

$$R^{1}$$
 + ONO + R^{3} CN $\frac{BF_{3} \cdot OEt_{2}}{rt}$ R^{1}

(f) This work: intramolecular redox cyclization

Scheme 1 Strategic access to cinnolines.

reaction was carried out in the mixed solvent i PrOH/H₂O (5:1) at 100 °C for 3 h (entry 3). Encouraged by this result, we continued to optimize the reaction conditions. Several bases, solvents, and temperatures were examined, and the results were summarized in Table 1. Remarkably, when the reaction was conducted in the presence of C_SOH·H₂O, the yield of 3aa was given to 56% (entry 4). Other bases (NaOH and LiOH) were found to give lower yields (entries 5 and 6). However, we did not detect the desired product when using some inorganic bases (K₂CO₃, Cs₂CO₃ and Na₂CO₃) and organic bases (DABCO, t-BuOK and DBU) (entries 7-12). Next, the amount of C_SOH·H₂O was examined (entries 13-15). The reaction could proceed smoothly with 59% yield, when only 3.0 equiv. of C_SOH·H₂O was used in the reaction (entry 15). Subsequently, examination of different mixed solvents (MeOH/H2O, DMSO/H2O, dioxane/ H₂O, EtOAc/H₂O, THF/H₂O and EtOH/H₂O) revealed that EtOH/ H₂O was the best choice for the reaction, and the corresponding yield increased to 63% (entries 16-21). Following the above investigations, the ratio of EtOH/H₂O was evaluated (entries 22– 26), and a higher yield (81%) was observed with the ratio 2:1 (entry 23). Temperature screening suggested that neither a rise nor a drop of the temperature promoted the reaction (entries 27 and 28).

After optimizing the reaction conditions, we explored the substrate scope of benzylamine (2), as shown in Table 2. It is

Table 1 Optimization of the reaction conditions^a

Entry	Solvent (ratio)		T (°C)	Yield ^b (%)	
		Base (equiv.)		3aa	4
1	ⁱ PrOH	KOH (20)	100	15	12
2	H_2O	KOH (20)	100	0	0
3	ⁱ PrOH/H ₂ O (5/1)	KOH (20)	100	36	20
4	ⁱ PrOH/H ₂ O (5/1)	$C_SOH \cdot H_2O$ (20)	100	56	19
5	ⁱ PrOH/H ₂ O (5/1)	NaOH (20)	100	35	21
6	ⁱ PrOH/H ₂ O (5/1)	LiOH (20)	100	42	10
7	ⁱ PrOH/H ₂ O (5/1)	$K_2CO_3(20)$	100	0	0
8	ⁱ PrOH/H ₂ O (5/1)	Cs_2CO_3 (20)	100	0	0
9	ⁱ PrOH/H ₂ O (5/1)	Na_2CO_3 (20)	100	0	0
10	ⁱ PrOH/H ₂ O (5/1)	DABCO (20)	100	0	0
11	ⁱ PrOH/H ₂ O (5/1)	t-BuOK (20)	100	0	0
12	ⁱ PrOH/H ₂ O (5/1)	DBU (20)	100	0	0
13	ⁱ PrOH/H ₂ O (5/1)	$C_SOH \cdot H_2O$ (10)	100	57	25
14	ⁱ PrOH/H ₂ O (5/1)	$C_SOH \cdot H_2O(5)$	100	55	27
15	ⁱ PrOH/H ₂ O (5/1)	$C_SOH \cdot H_2O(3)$	100	59	22
16	$MeOH/H_2O(5/1)$	$C_SOH \cdot H_2O(3)$	100	17	<5
17	$DMSO/H_2O(5/1)$	$C_SOH \cdot H_2O(3)$	100	<5	51
18	Dioxane/ $H_2O(5/1)$	$C_SOH \cdot H_2O(3)$	100	41	< 5
19	EtOAc/ $H_2O(5/1)$	$C_SOH \cdot H_2O(3)$	100	0	0
20	$THF/H_2O(5/1)$	$C_SOH \cdot H_2O(3)$	100	0	0
21	EtOH/ $H_2O(5/1)$	$C_SOH \cdot H_2O(3)$	100	63	31
22	EtOH/ $H_2O(3/1)$	$C_SOH \cdot H_2O(3)$	100	67	23
23	EtOH/ $H_2O(2/1)$	$C_SOH \cdot H_2O(3)$	100	81	<5
24	EtOH/ $H_2O(1/1)$	$C_SOH \cdot H_2O(3)$	100	73	<5
25	EtOH/ $H_2O(1/2)$	$C_SOH \cdot H_2O(3)$	100	<5	<5
26	EtOH/ $H_2O(1/3)$	$C_SOH \cdot H_2O(3)$	100	<5	< 5
27	EtOH/H ₂ O $(2/1)$	$C_SOH \cdot H_2O(3)$	90	70	11
28	EtOH/H ₂ O 2/1)	$C_SOH \cdot H_2O(3)$	110	74	<5

 $[^]a$ Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), **2a** (1.5 mmol, 3.0 equiv.), base (1.5 mmol, 3.0 equiv.) and solvent (6 ml) heated in oil bath for 3 h in sealed tube. b Isolated yields.

noteworthy that the electronic properties of the substituents on the aromatic ring system were shown to have a significant influence on the efficiency of this transformation. The benzylamine bearing electron-neutral (H) and electron-donating groups (2-Me, 3-Me, 4-Me, 3,4-2Me, 2-OMe, 4-OMe, -NH₂, 3,4-(OCH₂O)-) attached to the benzene ring, transformed smoothly into the corresponding products in moderate to good yields (53-81%; 3aa-3ai). Much to our satisfaction, halo-substituted (2-Br, 3-Br, 4-Br, 2-Cl, 4-Cl, 4-F, 4-I) substrates were also compatible, giving moderate yields (45-60%; 3aj-3ap). Fortunately, heterocyclic substituents (3-pyridyl, 4-pyridyl, 2-furyl, 2-thienyl) were also compatible, affording the expected products (3aq-3at) in 45-56% yields. In addition, naphthyl group substrates were also compatible, affording the expected products 3au and 3av in 46% and 50% yields, respectively. However, when the substrate was 2-aminoacetonitrile, the desired product 3ax was not afforded.

Table 2 Scope of benzylamine^a

OH NO ₂	* R ² NH ₂ —	CsOH·H₂O EtOH/H₂O, 100 °C	N^2N
N°N	Me N°N	Me N'N	Me N°N
3aa,81%	3ab, 62%	3ac, 66%	3ad, 67%
Me Me	MeO No	OMe N ^c N	NH ₂
3ae, 60%	3af, 79%	3ag, 80%	3ah, 53%
N°SN ST	Br N'N	Br N.N	Br
3ai 59%	3aj,51%	3ak, 54%	3a1 49%
CI N°N	CI N°N	F	CYN-N
3am , 48%	3an, 45%	3ao, 60%	3ap, 52%
N°N N	N ₂ N	CNN O	CYN'N S
3aq, 55%	3ar, 56%	3as, 45%	3at, 48%
N'N I	N: N	N'N	CN N'N
3au, 46%	3av, 50%	3av, 52%	3ax, 0%

^a Reaction conditions: **1a** (1.0 mmol, 1.0 equiv.), 2 (3.0 mmol, 3.0 equiv.) and $C_SOH \cdot H_2O$ (3.0 mmol, 3.0 equiv.) was stirred in EtOH/ H_2O (4 ml/2 ml) at 100 °C heated in oil bath for 3 h in sealed tube. Isolated yields.

Encouraged by the results described above, the scope of 2-nitrobenzyl alcohol (1) was subsequently examined (Table 3). At first, electron-donating substituted 2-nitrobenzyl alcohols 1b and 1c were explored, and the corresponding products 3ba and 3ca were obtained in 63% and 51% yields, respectively. Halosubstituted (2-Br, 4-Br, 2-Cl, 4-Cl, 5-Cl) groups substrates were also compatible, affording the expected products (45–50%;

Table 3 Scope of 2-nitrobenzyl alcohol^a

3da-3ha). In addition, when the substrate was secondary alcohol **1i**, the desired product **3ia** was not afforded.

To gain insights into the reaction process, control experiments were performed (Scheme 2). The reaction of 2-nitrobenzyl alcohol ${\bf 1a}$ converted to 2-nitrosobenzaldehyde ${\bf 5}$ in 33% yield under the standard conditions (eqn 1). Later, the reaction between compound ${\bf 5}$ and ${\bf 2a}$ proceeded to give the target product ${\bf 3aa}$ in 39% yield (eqn 2). To our surprise, when the reaction was carried out in EtOH/H₂O at $100\,^{\circ}$ C for 20 min in the presence of 3.0 equiv. $C_{\rm S}$ OH·H₂O, the desired product (${\bf 3aa}$) was obtained in 20% yield together with unexpected (E)-2-(2-benzylidenehydrazineyl) benzaldehyde ${\bf 6}$ (16%) (eqn 3). Moreover, compound ${\bf 6}$ converted to the desired product ${\bf 3aa}$ in excellent yield (90%) under standard conditions (eqn 4). These results identified that compounds ${\bf 5}$ and ${\bf 6}$ were very probably intermediates for this reaction.

On the basis of the above-mentioned experimental results, a possible mechanism for this reaction is proposed as shown in Scheme 3 (using **3aa** as an example). Initially, 2-nitrobenzyl alcohol **1a** undergoes deprotonation in the presence of $C_SOH \cdot H_2O$ to form 2-nitrosobenzaldehyde 5,¹⁷ which is generated *in situ via* intramolecular redox reaction. Subsequently, intermediate 5 reacts with benzylamine **2a** through a condensation reaction with elimination of H_2O to afford (*E*)-2-(benzyldiazenyl)benzaldehyde **C**. Meanwhile, *ortho*-azo intermediate **C** is isomerized to form (*E*)-2-(2-benzylidenehydrazineyl) benzaldehyde **6**. Subsequently, hydrazone **6** undergoes an intramolecular cyclization process to afford intermediate **D**. Finally, intermediate **D** is converted to the desired product **3aa** through an aromatization reaction with elimination of H_2O .

In order to demonstrate the potential applications for organic synthesis, the reaction of 2-nitrobenzyl alcohol (1a) and benzylamine (2a) was performed on a gram scale (Scheme 4). To our satisfaction, the reaction was carried out very well, and the 3aa was furnished in 57% yield.

Scheme 2 Control experiments.

^a Reaction conditions: 1 (0.5 mmol, 1.0 equiv.), 2a (1.5 mmol, 3.0 equiv.) and $C_8OH \cdot H_2O$ (1.5 mmol, 3.0 equiv.) was stirred in EtOH/ H_2O (4 ml/2 ml) at 100 °C heated in oil bath for 3 h in sealed tube. Isolated yields.

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Scheme 3 A possible mechanism

Scheme 4 Gram scale experiment

In summary, we have developed a novel transition-metal-free intramolecular redox cyclization reaction for the efficient synthesis of cinnoline derivatives by simple treatment with C_S-OH·H₂O in EtOH/H₂O. This method obtained 2-nitrobenzaldehyde intermediate by intramolecular redox reaction of 2-nitrobenzyl alcohol, which then condenses with benzylamine, followed by azo is isomerized to form hydrazone, cyclization, and aromatization processes to form cinnoline compounds. Further studies on this method for the synthesis of other bioactive compounds and applications are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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