## PAPER

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

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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.

Cinnolines are important nitrogen-containing heterocyclic organic compounds which have attracted widespread attention in the field of organic, materials and pharmaceutical chemistry.[1] They are known to display interesting biological activities such as inhibitory activity toward CSF-1R,[2] antitumor,[3] antiviral,[4] anti-inflammatory[5] and sedative effects[6] (Fig. 1).

The classical synthetic approaches to cinnolines start from N-phenylhydrazones or N-phenylazo compounds via Rh-catalyzed C–H activation,[7] Pd-catalyzed annulation,[8] or Cu-catalyzed C–H functionalization/cyclization strategies.[9] For example, in 2012, Ge's group reported a Cu-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of N-methyl-N-phenylhydrazones for the formation of cinnolines (Scheme 1a).[10] Subsequently, Lin and coworkers described a Rh-catalyzed 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 transition-metal-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 (Scheme 1f).

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 H$_2$O (entry 2). Intriguingly, the yield of 3-phenylcinnoline (**3aa**) was increased to 36% when the

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Fig. 1 Bioactive cinnoline derivatives.

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

CuSO$_4$, CuI
pyridine, CF$_3$SO$_3$H
O$_2$, DMF, 110 °C
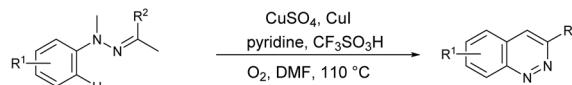
(b) Lin's work: Rh-catalyzed redox-neutral annulation

[RhCp*Cl$_2$]$_2$/AgSbF$_6$
PivOH/DCE, 50 °C

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

Cu(OAc)$_2$·H$_2$O
toluene, air, 110 °C

X= F, OCH$_3$, N(CH$_3$)$_2$
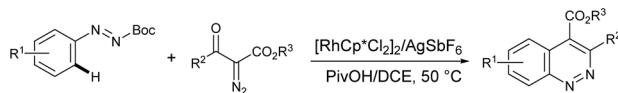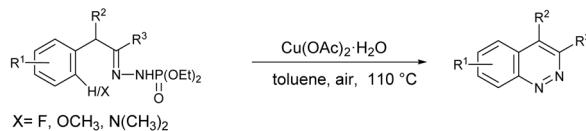
(d) Wang's work: Cu-catalyzed cyclization

Cu(OAc)$_2$
DCE/CH$_3$OH, 40 °C
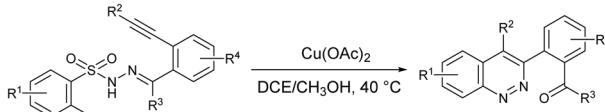
(e) Wang's work: BF$_3$-ehterate-promoted cascade reaction

BF$_3$·OEt$_2$
rt
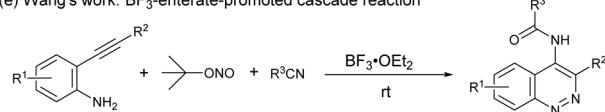
(f) This work: intramolecular redox cyclization

CsOH·H$_2$O
EtOH/H$_2$O, 100 °C
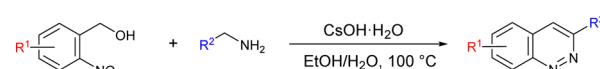
**Scheme 1** Strategic access to cinnolines.

reaction was carried out in the mixed solvent $^i$PrOH/H$_2$O (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$_S$OH·H$_2$O, 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 (K$_2$CO$_3$, Cs$_2$CO$_3$ and Na$_2$CO$_3$) and organic bases (DABCO, *t*-BuOK and DBU) (entries 7–12). Next, the amount of C$_S$OH·H$_2$O was examined (entries 13–15). The reaction could proceed smoothly with 59% yield, when only 3.0 equiv. of C$_S$OH·H$_2$O was used in the reaction (entry 15). Subsequently, examination of different mixed solvents (MeOH/H$_2$O, DMSO/H$_2$O, dioxane/H$_2$O, EtOAc/H$_2$O, THF/H$_2$O and EtOH/H$_2$O) revealed that EtOH/H$_2$O 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/H$_2$O 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]
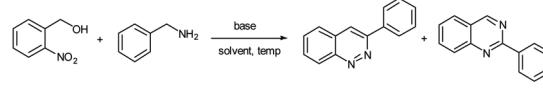
|  |  |  |  | Yield[b] (%) | |
| Entry | Solvent (ratio) | Base (equiv.) | T (°C) | **3aa** | **4** |
| --- | --- | --- | --- | --- | --- |
| 1 | $^i$PrOH | KOH (20) | 100 | 15 | 12 |
| 2 | H$_2$O | KOH (20) | 100 | 0 | 0 |
| 3 | $^i$PrOH/H$_2$O (5/1) | KOH (20) | 100 | 36 | 20 |
| 4 | $^i$PrOH/H$_2$O (5/1) | C$_S$OH·H$_2$O (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$_2$CO$_3$ (20) | 100 | 0 | 0 |
| 8 | $^i$PrOH/H$_2$O (5/1) | Cs$_2$CO$_3$ (20) | 100 | 0 | 0 |
| 9 | $^i$PrOH/H$_2$O (5/1) | Na$_2$CO$_3$ (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$_S$OH·H$_2$O (10) | 100 | 57 | 25 |
| 14 | $^i$PrOH/H$_2$O (5/1) | C$_S$OH·H$_2$O (5) | 100 | 55 | 27 |
| 15 | $^i$PrOH/H$_2$O (5/1) | C$_S$OH·H$_2$O (3) | 100 | 59 | 22 |
| 16 | MeOH/H$_2$O (5/1) | C$_S$OH·H$_2$O (3) | 100 | 17 | <5 |
| 17 | DMSO/H$_2$O (5/1) | C$_S$OH·H$_2$O (3) | 100 | <5 | 51 |
| 18 | Dioxane/H$_2$O (5/1) | C$_S$OH·H$_2$O (3) | 100 | 41 | <5 |
| 19 | EtOAc/H$_2$O (5/1) | C$_S$OH·H$_2$O (3) | 100 | 0 | 0 |
| 20 | THF/H$_2$O (5/1) | C$_S$OH·H$_2$O (3) | 100 | 0 | 0 |
| 21 | EtOH/H$_2$O (5/1) | C$_S$OH·H$_2$O (3) | 100 | 63 | 31 |
| 22 | EtOH/H$_2$O (3/1) | C$_S$OH·H$_2$O (3) | 100 | 67 | 23 |
| **23** | **EtOH/H$_2$O (2/1)** | **C$_S$OH·H$_2$O (3)** | **100** | **81** | **<5** |
| 24 | EtOH/H$_2$O (1/1) | C$_S$OH·H$_2$O (3) | 100 | 73 | <5 |
| 25 | EtOH/H$_2$O (1/2) | C$_S$OH·H$_2$O (3) | 100 | <5 | <5 |
| 26 | EtOH/H$_2$O (1/3) | C$_S$OH·H$_2$O (3) | 100 | <5 | <5 |
| 27 | EtOH/H$_2$O (2/1) | C$_S$OH·H$_2$O (3) | 90 | 70 | 11 |
| 28 | EtOH/H$_2$O 2/1 | C$_S$OH·H$_2$O (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, –NH$_2$, 3,4-(OCH$_2$O)–) 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]



3aa, 81%; 3ab, 62%; 3ac, 66%; 3ad, 67%; 3ae, 60%; 3af, 79%; 3ag, 80%; 3ah, 53%; 3ai 59%; 3aj, 51%; 3ak, 54%; 3al 49%; 3am, 48%; 3an, 45%; 3ao, 60%; 3ap, 52%; 3aq, 55%; 3ar, 56%; 3as, 45%; 3at, 48%; 3au, 46%; 3av, 50%; 3aw, 52%; 3ax, 0%
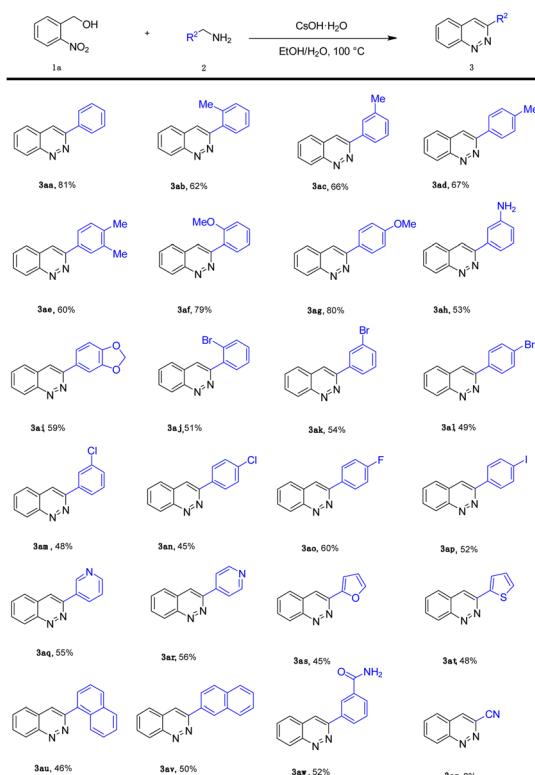
[a] Reaction conditions: **1a** (1.0 mmol, 1.0 equiv.), **2** (3.0 mmol, 3.0 equiv.) and $C_5OH \cdot H_2O$ (3.0 mmol, 3.0 equiv.) was stirred in EtOH/$H_2O$ (4 ml/2 ml) at 100 °C heated in oil bath for 3 h in sealed tube. Isolated yields.

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. Halo-substituted (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]



3ba, 63%; 3ca, 51%; 3da, 48%; 3ea, 50%; 3fa, 48%; 3ga, 49%; 3ha, 45%; 3ia, 0%
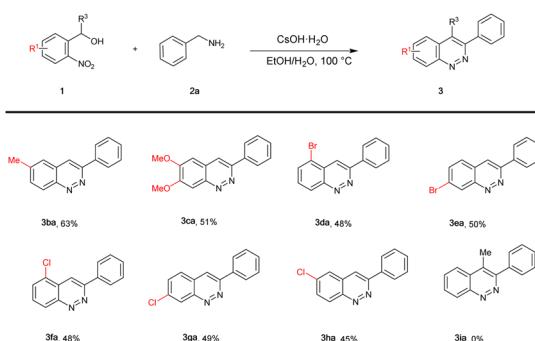
[a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), **2a** (1.5 mmol, 3.0 equiv.) and $C_5OH \cdot H_2O$ (1.5 mmol, 3.0 equiv.) was stirred in EtOH/$H_2O$ (4 ml/2 ml) at 100 °C heated in oil bath for 3 h in sealed tube. Isolated yields.

**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-nitro-benzyl alcohol **1a** converted to 2-nitrosobenzaldehyde **5** in 33% yield under the standard conditions (eqn 1). Later, the reaction between compound **5** and **2a** proceeded to give the target product **3aa** in 39% yield (eqn 2). To our surprise, when the reaction was carried out in EtOH/$H_2O$ at 100 °C for 20 min in the presence of 3.0 equiv. $C_5OH \cdot H_2O$, the desired product (**3aa**) was obtained in 20% yield together with unexpected (*E*)-2-(2-benzy-lidenehydrazineyl) benzaldehyde **6** (16%) (eqn 3). Moreover, compound **6** converted to the desired product **3aa** in excellent yield (90%) under standard conditions (eqn 4). These results identified that compounds **5** and **6** were very probably inter-mediates 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 $C_5OH \cdot H_2O$ to form 2-nitrosobenzaldehyde **5**,[17] which is gener-ated *in situ via* intramolecular redox reaction. Subsequently, intermediate **5** reacts with benzylamine **2a** through a conden-sation reaction with elimination of $H_2O$ to afford (*E*)-2-(benzyl-diazenyl)benzaldehyde **C**. Meanwhile, *ortho*-azo intermediate **C** is isomerized to form (*E*)-2-(2-benzylidenehydrazineyl) benzal-dehyde **6**. Subsequently, hydrazone **6** undergoes an intra-molecular 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.
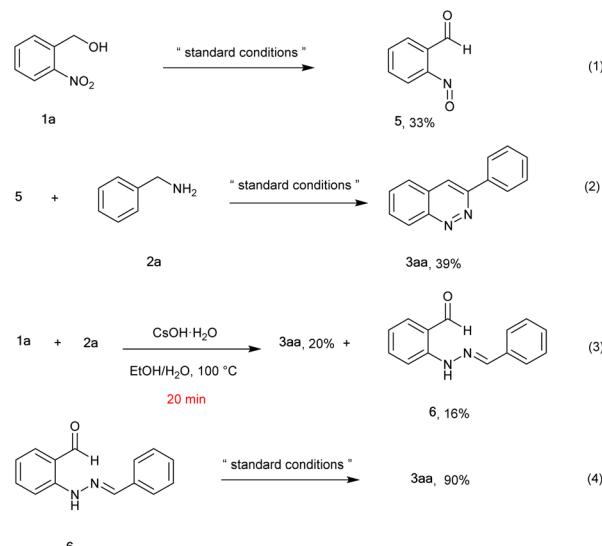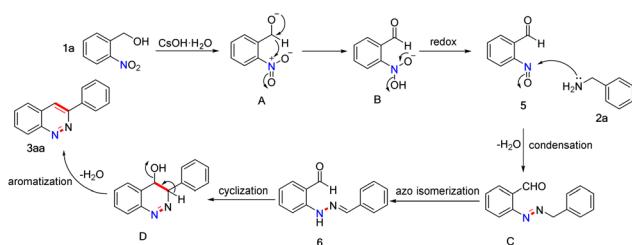
**Scheme 3** A possible mechanism.
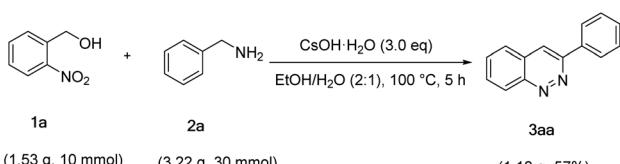


**Scheme 4** Gram scale experiment.

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·$H_2O$ in EtOH/$H_2O$. 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.

## Acknowledgements

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