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An integration of condensation/Ullmann-type coupling/bicyclization sequences: copper-catalyzed three-component direct synthesis of [1,2,4]triazolo[1,5-*b*]isoquinolin-5(1*H*)-ones†

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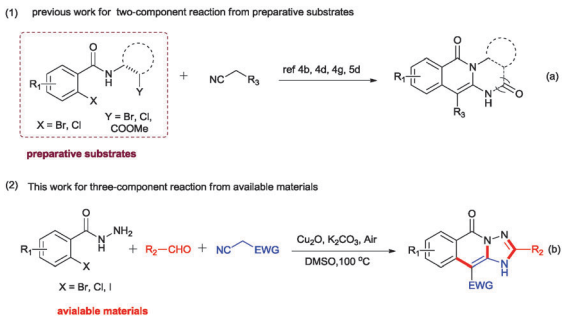
A highly efficient three-component domino protocol has been developed for the synthesis of [1,2,4]triazolo[1,5-*b*]isoquinolin-5(1*H*)-ones from simple and readily available *o*-halogenated benzohydrazides, aldehydes and nitriles. This domino process involves sequential selective condensation, copper-catalyzed intermolecular C-arylation and bicyclization. Notably, the use of ligands and anaerobic conditions can be avoided in this reaction.

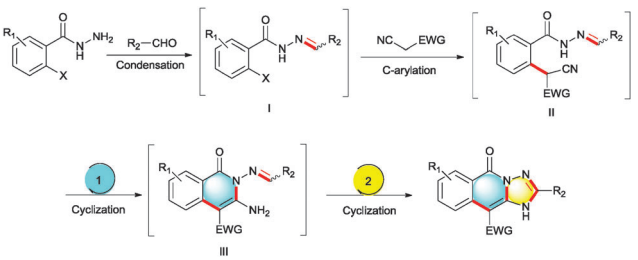
Up to now, the major goal of synthetic chemists has been to design an elegant and efficient synthetic route for the construction of desired products from simple molecules.[1] So maximizing efficiency and minimizing steps in the synthesis of target molecules is where synthetic chemists concentrate their efforts in the integration of some organic unit reactions by a domino or self-sequence strategy.[2] Recently, great progress has been achieved in Ullmann-type coupling reactions.[3] Notably, many types of fused N-heterocycles have also been constructed *via* elegant domino processes driven by copper-catalyzed cross-coupling, as reported by Fu's group[4] and others.[5] These routes, however, implied a multistep process since the starting materials were not readily available and needed to be prefabricated (Scheme 1a). Herein, we report a direct and efficient synthesis of novel fused N-heterocycles *via* an integration of condensation/Ullmann-type coupling/bicyclization sequences from simple and readily available *o*-halogenated benzohydrazides, aldehydes and nitriles (Scheme 1b).

Isoquinolinones and 1,2,4-triazolo[1,5-*a*]pyridines are two important subclasses of N-heterocycles. Many compounds containing isoquinolinone[6] or 1,2,4-triazolo[1,5-*a*]pyridine[7] motifs exhibit various biological and medicinal activities. It is assumed that the hybrid structure containing both isoquinolinone and 1,2,4-triazolo-[1,5-*a*]pyridine motifs may feature promising bioactivity for screening. To the best of our knowledge, there is no report on direct construction of this novel skeleton *via* a domino strategy from simple materials in one-pot. We herein envision a concise three-component domino strategy to synthesize [1,2,4]triazolo[1,5-*b*]isoquinolin-5(1*H*)-ones through a rational design using *o*-halogenated benzohydrazides as the initial building blocks. In our hypothesis, *o*-halogenated benzohydrazides could react preferentially with aldehydes over nitriles to afford *o*-halogenated benzoyl hydrazones **I**, and then skeleton **I** might serve as a novel coupling partner trapped by nitriles to provide the key intermediate **II**. Intermediate **II** would undergo a facile cyclization to generate intermediate **III**. The desirable target molecules would be obtained after another cyclization (Scheme 2).

To test the above hypothesis, our investigation was initiated with 2-bromobenzohydrazide (**1a**), benzaldehyde (**2a**) and methyl



Scheme 1 Synthesis of fused N-heterocycles *via* a copper-catalyzed domino strategy involving nitriles.



Scheme 2 Rational design for synthesis of [1,2,4]triazolo[1,5-*b*]isoquinolin-5(1*H*)-ones *via* a domino strategy.

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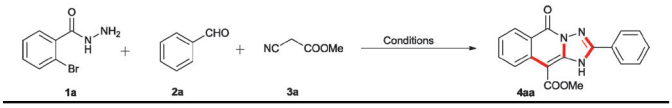
Table 1 Optimization of the reaction conditions[a,b]



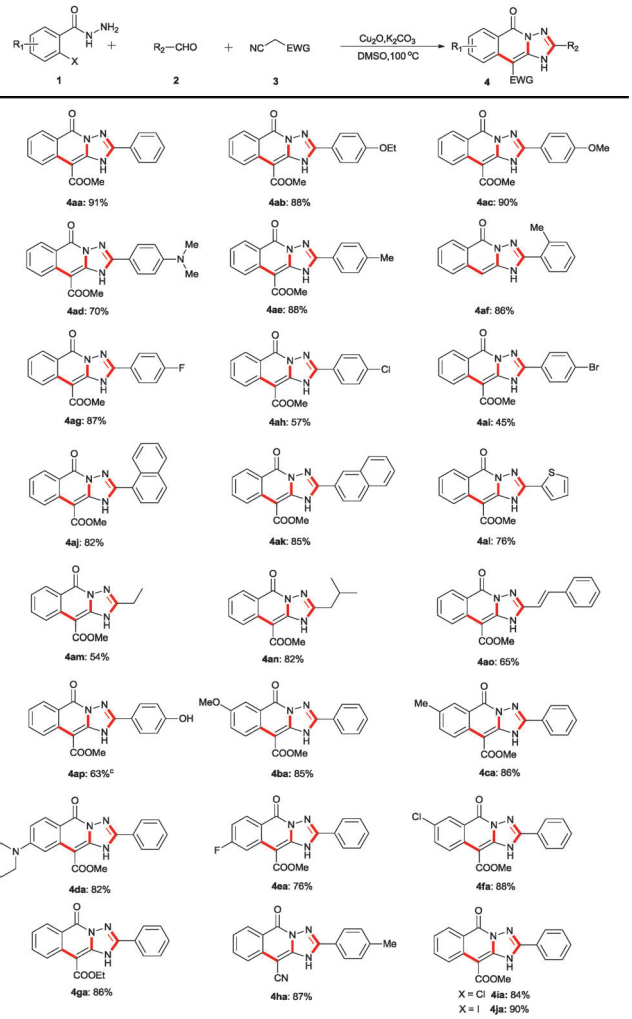
Entry	Catalyst	Base	Sovlent	Temp. (°C)	Yield[b] (%)
1	CuI	K_2CO_3	DMSO	100	84
2	CuI	Cs_2CO_3	DMSO	100	83
3	CuI	$NaHCO_3$	DMSO	100	80
4	CuI	KOH	DMSO	100	76
5	CuI	K_3PO_4	DMSO	100	74
6	CuCl	K_2CO_3	DMSO	100	86
7	CuBr	K_2CO_3	DMSO	100	86
8	**Cu_2O**	**K_2CO_3**	**DMSO**	**100**	**91**
9	$CuCl_2$	K_2CO_3	DMSO	100	62
10	$CuBr_2$	K_2CO_3	DMSO	100	68
11	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMSO	100	67
12	$Cu(OTf)_2$	K_2CO_3	DMSO	100	80
13	Cu_2O	K_2CO_3	DMF	100	88
14	Cu_2O	K_2CO_3	Toluene	100	Trace
15	Cu_2O	K_2CO_3	Dioxane	100	48
16	Cu_2O	K_2CO_3	DMSO	80	88
17	Cu_2O	K_2CO_3	DMSO	110	90

[a] Reactions conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), catalyst (10%) and base (0.75 mmol) were heated in 4 mL solvent in a sealed vessel under air for 10 h. [b] Isolated yields.

2-cyanoacetate (**3a**) as the model substrates for the optimization of the reaction conditions (Table 1). Various catalysts, bases, temperatures and solvents were examined, and all cases are shown in Table 1. To our delight, the reaction of 2-bromobenzohydrazide (**1a**) with benzaldehyde (**2a**) and methyl 2-cyanoacetate (**3a**) proceeded smoothly with 84% yield in the presence of CuI (0.1 equiv.) and K_2CO_3 (1.5 equiv.) at 100 °C in DMSO in a sealed vessel under air for 10 hours (Table 1, entry 1). Then, a series of bases was screened for this reaction, such as Cs_2CO_3, $NaHCO_3$, KOH, and K_3PO_4 (Table 1, entries 2–5), and the desired product **4aa** was also obtained in a good yield (74–83%). Next, various copper salts were screened against the reaction (Table 1, entries 6–12), and Cu_2O showed the highest activity (entry 8). Moreover, several solvents were tested (Table 1, entries 13–15), and DMSO was proved to be the most effective solvent (compare entries 8 and 13–15). Increasing or decreasing the temperature of the reaction did not lead to any further improvements in the yield (Table 1, entries 16 and 17).

Under the optimal conditions, the scope of aldehydes was investigated. As shown in Table 2, the reaction demonstrated good compatibility with various aldehydes. Reactions with aromatic aldehydes containing electron-neutral (H) and electron-donating (2-Me, 4-Me, 4-OEt, 4-OMe, and 4-(N-Me)$_2$) groups proceeded smoothly to afford the corresponding products in good to excellent yields (Table 2, **4aa–4af**, 70–91%). Halo-substituted aldehydes also gave target products **4ag–4ai** in 45% to 87% yields. To our delight, other representative aromatic aldehydes such as 1-naphthaldehyde, 2-naphthaldehyde and thiophene-2-carbaldehyde were also found to be suitable for this transformation and the desired products were obtained in satisfactory yields (Table 2, **4aj–4al**, 76–85%). Alkyl and conjugated aldehydes, including propaldehyde (**2m**), isovaleraldehyde (**2n**) and cinnamaldehyde (**2o**), also performed well to give the corresponding products in good yields (Table 2, **4am–4ao**, 54–82%). In addition, sensitive 4-hydroxybenzaldehyde

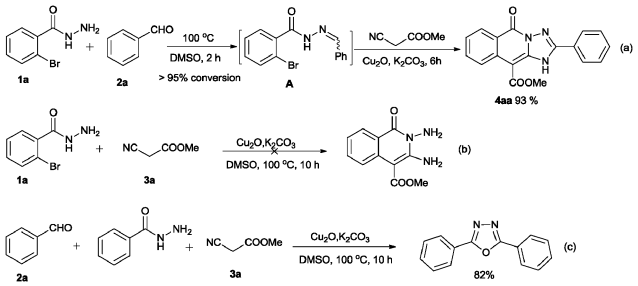
Table 2 Scope of aldehydes, 2-halobenzohydrazides and nitriles[a,b]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol) Cu_2O (0.05 mmol) and K_2CO_3 (0.75 mmol) in DMSO (4 mL) at 100 °C in a sealed vessel under air for 6–10 h; **1a–1g** (2-bromobenzohydrazides). [b] Isolated yields. [c] Reaction conditions: **1a** (0.5 mmol) and **2p** (0.5 mmol) were heated in DMSO (4 mL) at 100 °C in a sealed vessel under air for 1 h and then **3a** (0.5 mmol), Cu_2O (0.05 mmol) and K_2CO_3 (0.75 mmol) were added and the resulting mixture was stirred for another 6 h.

could transform into the desired product **4ap** in 63% yield when a one-pot two-step procedure was adopted.

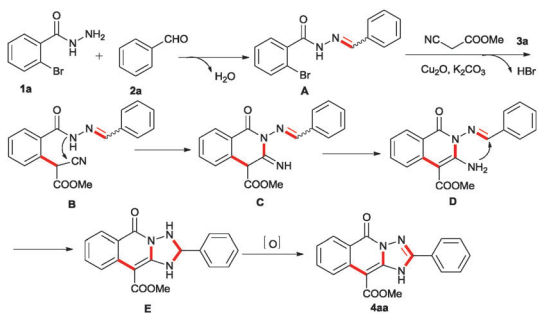
To further expand the scope of the substrates, a variety of 2-halobenzohydrazides and nitriles were examined. Gratifyingly, the attachment of an electron-donating or electron-withdrawing group to the phenyl group of **1** was well tolerated, with the corresponding products being obtained in good yields (Table 2, **4ba–4fa**, 76–88%). Moreover, ethyl 2-cyanoacetate (**3b**) and malononitrile (**3c**) could also be successfully applied to the transformation to generate target products in 86% and 87% yields, respectively (Table 2, **4ga** and **4ha**). In addition, 2-chlorobenzohydrazide (**1g**) and 2-iodobenzohydrazide (**1h**) also exhibit good reactivity under the optimized conditions (Table 2, **4ia** and **4ja**, 84% and 90%). Furthermore, the structure of **4ga** was unambiguously determined by X-ray crystallographic analysis (see ESI†).



Scheme 3 Control experiments.

To gain some insight into the mechanism of the domino process, several control experiments were performed as shown in Scheme 3. A one-pot two-step strategy was initially adopted in which 2-bromobenzohydrazide (**1a**) and benzaldehyde (**2a**) were heated in DMSO at 100 °C until disappearance of reactants (monitored by TLC), then methyl 2-cyanoacetate (**3a**), Cu_2O and K_2CO_3 were added and the resulting mixture was stirred for another 6 h to give the target product in 93% yield (Scheme 3(a)). This clearly demonstrated that hydrazone **A** may be a key intermediate in this transformation. When reaction of 2-bromobenzohydrazide (**1a**) and methyl 2-cyanoacetate (**3a**) was investigated under standard conditions, the reaction turned out to be a complex one with none of the desired coupling products being observed (Scheme 3(b)). Furthermore, a competition experiment was also conducted to clarify the reactivity of 2-bromobenzohydrazide (**1a**) and methyl 2-cyanoacetate (**3a**) towards benzaldehyde (**2a**), where benzohydrazide was reacted with methyl 2-cyanoacetate (**3a**) and benzaldehyde (**2a**) under standard conditions. To our surprise, 2,5-diphenyl-1,3,4-oxadiazole was obtained in 82% yield (Scheme 3(c)).[8] The results of these two control experiments indicate that the reaction was initiated by the condensation of aldehydes and *o*-halogenated benzohydrazides, rather than the cross-coupling between *o*-halogenated benzohydrazides and nitriles.

On the basis of the above results, a possible mechanism of the present reaction was proposed using 2-bromobenzohydrazide (**1a**), benzaldehyde (**2a**) and methyl 2-cyanoacetate (**3a**) as an example (Scheme 4). Initially, substrate 2-bromobenzohydrazide (**1a**) preferentially condensed with benzaldehyde (**2a**) to afford intermediate hydrazone **A**. Subsequently, copper-catalyzed Ullmann-type coupling of hydrazone **A** and methyl 2-cyanoacetate (**3a**) would proceed easily to give **B** in the presence of a base (K_2CO_3) in the light of the *ortho*-substituent effect,[4a,d] then intramolecular addition of NH with CN in **B** leads to **C**, and transfer of the double bond in **C** affords **D**. Next, another nucleophilic attack of nitrogen to imine afforded **E** (intermediate **E** was detected by MS, see the ESI†). Finally, the target product **4aa** was obtained after final oxidative dehydrogenation.



Scheme 4 Possible mechanism.

In conclusion, we have developed a highly efficient three-component domino protocol for the synthesis of [1,2,4]triazolo[1,5-*b*]-isoquinolin-5(1*H*)-ones using readily available *o*-halogenated benzohydrazides, aldehydes and nitriles as basic building blocks. This domino process involves sequential selective condensation, copper-catalyzed intermolecular C-arylation, intramolecular addition of NH with CN, nucleophilic attack of amino to imine and final oxidative dehydrogenation. It is notable that the reaction performs well with varying functional group tolerance in the absence of a ligand under air. Due to the above mentioned characteristics of this reaction, it should be of great utility for concise construction of complex and diverse fused N-heterocycles for organic chemistry and medicinal chemistry. Further studies on the applications of this strategy will be reported in due course.

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