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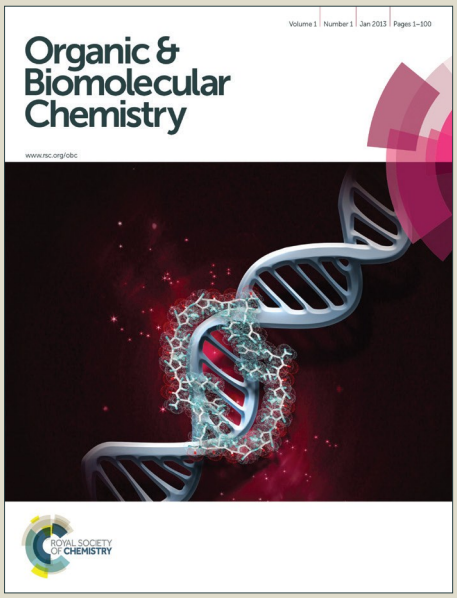

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COMMUNICATION

Ligand-free Cu-Catalyzed [3+2] Cyclization for the Synthesis of Pyrrolo[*1,2-a*]quinolines with Ambient Air as Terminal Oxidant

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A ligand-free Cu-catalyzed [3+2] cycloaddition of ethyl 2-(quinolin-2-yl)acetates, ethyl 2-(isoquinolin-1-yl)acetates, and ethyl 2-(pyridin-2-yl)acetates with (*E*)-chalcones for a "one-pot" synthesis of pyrrolo[1,2-a]quinolines, pyrrolo[2,1-a]isoquinolines and indolizines has been developed. The annulation products were isolated in moderate to good yields with air as the sole oxidant under the mild conditions.

Transition-metal-catalyzed oxidative C-H amination reaction via C-H activation is one of the most demanding procedures to form C-N bonds.[1] Cross dehydrogenative coupling (CDC) reaction using direct C-H bond activation strategy, which is a powerful method for constructing C-N bonds, would eliminate prefunctionalization and make synthetic schemes shorter.[2] Various late transition metal catalysts such as Pd,[3] Ru,[4] Rh,[5] Ir,[6] Cu[7] have been applied in CDC reactions. However, comparing to other late transition metals, copper salt is low-costed and low-toxic. Therefore, Cu-catalyzed CDC reactions between C-H and N-H bonds have received significant interest over the recent decades.[7,8] In Cu-catalyzed CDC reactions, oxidant plays an important role and has been widely employed, such as hypervalent iodine reagents, peroxides, MnO_2, $K_2S_2O_8$ etc.. On the other hand, chemists lay emphasis on green and sustainable manufacturing in order to solve problems of environmental pollution and resource shortage. Therefore, air or O_2, which has environment-friendly and inexpensive characters existing in the nature, has been widely used as an oxidant.[9]

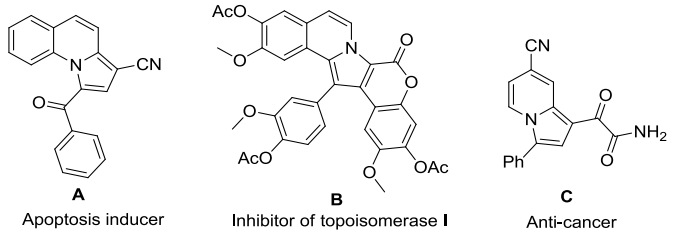

Fig 1 Pyrrolo[*1,2-a*]quinoline, pyrrolo[*2,1-a*]isoquinoline and indolizine derivatives with biological activities.

Pyrrolo[*1,2-a*]quinolines, pyrrolo[*2,1-a*]isoquinolines and indolizines and their derivatives are important classes of *N*-containing heterocycles occurring in numerous pharmaceuticals,[10] natural products,[11] and functional materials.[12] For example, pyrrolo[*1,2-a*]quinoline compound **A** has been investigated extensively to induce apoptosis which plays a key role for the maintenance of cell homeostasis.[13] pyrrolo[*2,1-a*]isoquinoline compound **B** (Lamellarin **D**) is a potent inhibitor of topoisomerase **I** as a selective HIV integrase inhibitor.[14] Indolizine compound **C** could inhibit carcinoma cell's proliferation (Fig. 1).[15] The synthesis of these derivatives has received a lot of progress.[16] Recently, some [3+2] reactions were reported by Jia[17], and Adimurthy[18] groups to synthesize indolizines from ethyl 2-(pyridin-2-yl)acetates and unsaturated double bonds. However, equivalents of copper salt or inorganic oxidants were used in these reactions. Moreover, other heterocycles such as quinoline, isoquinoline and

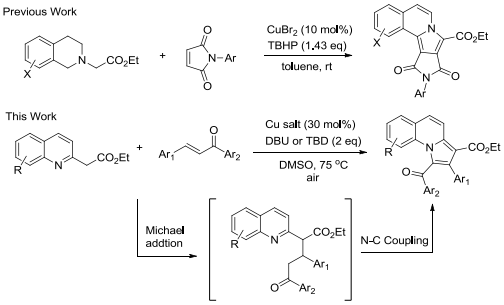

Fig. 2 Tandem Michael additon-oxidative cyclization for the synthesis of pyrrolo[*1,2-a*]quinolones.

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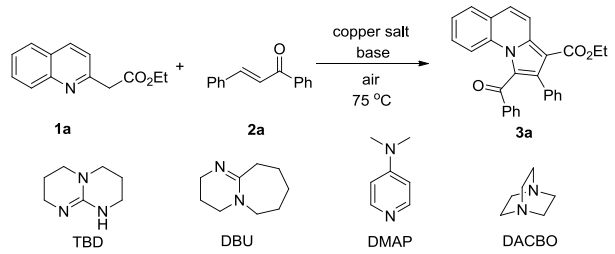
Table 1 Optimization of reaction conditions[a]



Entry	Cat.	Base	Solvent	Yield (%)[b]
1	$Cu(OAc)_2$	TBD	DMSO	44
2	$Cu(OAc)_2$	DBU	DMSO	81
3	$Cu(OAc)_2$	DMAP	DMSO	trace
4	$Cu(OAc)_2$	DABCO	DMSO	trace
5	$Cu(OAc)_2$	DBU	toluene	5
6	$Cu(OAc)_2$	DBU	DCE	trace
7	$Cu(OAc)_2$	DBU	dioxane	17
8	$CuBr_2$	DBU	DMSO	36
9	CuI	DBU	DMSO	59
10	$Cu(OTf)_2$	DBU	DMSO	54
11	CuCl	DBU	DMSO	34
12[c]	$Cu(OAc)_2$	DBU	DMSO	61
13[d]	$Cu(OAc)_2$	DBU	DMSO	35
14[e]	$Cu(OAc)_2$	DBU	DMSO	67

[a] Unless specified, a mixture of ethyl 2-(quinolin-2-yl)acetate **1a** (2.0 mmol) and (*E*)-chalcone **2a** (4.0 mmol) in the presence of copper salt (30 mol%) and base (2 equiv) in solvent (1.0 mL) was stirred at 75 °C for 18 h. [b] Isolated yields. [c] Reaction was carried for 12 h. [d] 0.15 equiv $Cu(OAc)_2$ was used. [e] 1 equiv of DBU was used.

benzo[*f*]quinoline have not been tested. Recently, our research interest is focused on C-N bond formation methodologies.[19] In 2011, our group developed a very efficient methodology to synthesize pyrrolo[*2,1-a*]isoquinoline derivatives.[20] Herein, to continue our research, we reported a simple and practical [3+2] annulation reaction via Michael addition-oxidative cyclization by using ambient air as terminal oxidant (Fig. 2).

We initiated our investigation with the cyclization of ethyl 2-(quinolin-2-yl)acetate **1a** (0.2 mmol) and (*E*)-chalcone **2a** (0.4 mmol) in DMSO as the modal reaction in the presence of $Cu(OAc)_2$ (0.06 mmol) and 2,3,4,6,7,8-hexahydro-1*H*-pyrimido[*1,2-a*]pyrimidine (TBD) (0.4 mmol), which is a good catalyst for Michael addition.[21] Fortunately, the desired [3+2] product **3a** was obtained in 44% yield after 18h at 75 °C (Table 1, entry 1). When DBU was used as the base, the yield of product **3a** was increased to 81% (entry 2). Then other organic bases were screened, DMAP and DABCO were found to be ineffective (entries 3 and 4). The solvent screening revealed that toluene and DCE afforded the products with poor yields (entries 5 and 6). Dioxane gave a slightly higher yield than toluene (17%, entry 7). The results showed that DMSO was the most suitable solvent for the reaction. When different copper

Table 2 Copper-catalyzed aerobic oxidative [3+2] cyclization for the synthesis of pyrrolo[*1,2-a*]quinolines[a]

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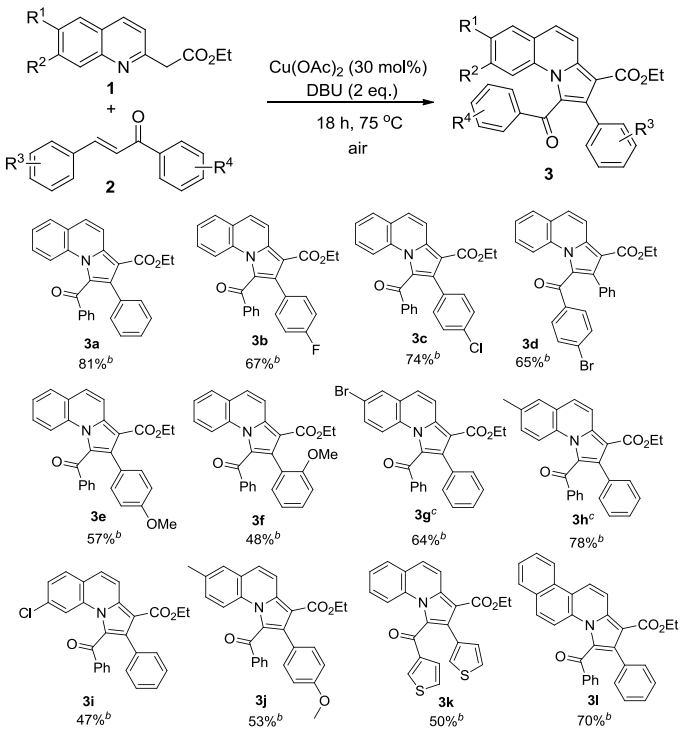
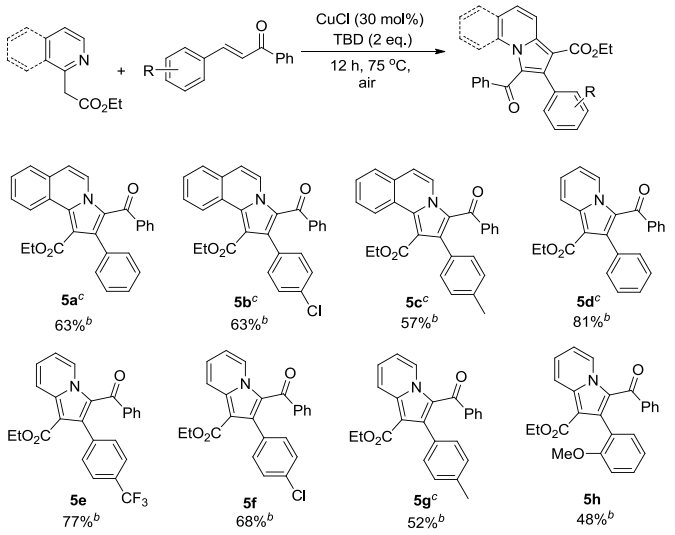


[a] Unless otherwise noted, the reaction was carried out by using **1** (0.2 mmol), **2** (0.4 mmol), $Cu(OAc)_2$ (0.06 mmol) and DBU (0.4 mmol) in DMSO (1 mL) at 75 °C for 18 h. [b] Isolated yield. [c] With CuCl and TBD (see SI).

salts were screened, CuI, $Cu(OTf)_2$, $CuBr_2$, and CuCl were less effective than $Cu(OAc)_2$ (entries 8-11). What's more, when the reaction was carried out for 12 h, the reaction yield was decreased to 61% (entry 12). Further lowering of the catalyst loading to 15 mol%, the yield was decreased to 35% (entry 13). Decreasing the equivalent of DBU also resulted the lower yield (67%, entry 14).

After optimizing the reaction conditions, we examined the scope of a variety of 2-(quinolin-2-yl)acetates **1** and (*E*)-chalcones **2**. As shown in Table 2, almost all of the tested combinations produced the desired pyrrolo[*1,2-a*]quinolines with moderate to good isolated yields. Both electron-withdrawing and electron-donating substituents on the (*E*)-chalcones and 2-(quinolin-2-yl)acetates were tolerated in this reaction. Generally, electron-withdrawing groups on the benzene ring of (*E*)-chalcones have positive effects on the yield due to their capacity to elevate the activity of (*E*)-chalcones (Table 2, **3b**-**3d**). The reaction gave lower yields when R^3 was *para*-OMe (**3e**) and *ortho*-OMe (**3f**), this implied that electronic effect and steric effect had an influence on the reaction. Furthermore, the results also revealed that quinolines carrying a substituent group at C-6 or C-7 afforded the corresponding products in generally acceptable to good yields. It is worth mentioning that the reactions gave poor yields when Br or CH_3 were substitutes at C-6 in $Cu(OAc)_2$/DBU system. However, when the catalyst system was changed to CuCl as the catalyst and TBD as the base, the reactions proceeded smoothly with

Table 3 Copper-catalyzed aerobic oxidative [3+2] cyclization for the synthesis of pyrrolo[*2,1-a*]isoquinolines and indolizines[a]



[a] Unless otherwise noted, the reaction was carried out by using **1** (0.2 mmol), **2** (0.4 mmol), $Cu(OAc)_2$ (0.06 mmol) and DBU (0.4 mmol) in DMSO (1 mL) at 75 °C for 18 h. [b] Isolated yield. [c] With CuCl and TBD (see SI).

the yield of 64% and 78% (**3g** and **3h**). Additionally, the yield would be as low as 47% when Cl was at C-7 (**3i**). Product **3j** with double electron donating groups (R^1 = Me, R^2 = *ortho*-OMe) was well tolerated with 52% yield. Besides, thienyl was also a compatible substrate with the formation of product **3k** in 50% yield. Moreover, the benzo[*f*]quinoline's derivative reacted well to give the desired product **3l** in 70% yield.

To further expand the scope of the reaction, ethyl 2-(isoquinolin-3-yl)acetate and ethyl 2-(pyridin-2-yl-acetate were investigated (Table 3). The catalytic system of the combination of CuCl as catalyst and TBD as base afforded higher yields for most substrates (**5a**-**5d**, **5g**). Similarly, the (*E*)-chalcone with neutral or electron-withdrawing substitutions at the *para*-position of the benzene ring gave slightly higher yield (**5a**, **5b**, **5d**-**5f**). While electron-donating groups afforded lower yields (**5c**, **5g**). Moreover, when the substituted group was changed to *ortho*-OMe, the yield was decreased to 48% (**5h**).

Coumarins play crucial roles in natural products and they exhibit a broad pharmacological profile such as antitumor activity,[22] HIV-1 protease,[23] and inhibition of antidiabetic.[24] To test the usefulness of our methodology, demethylation of the methoxy group of **5h** by BBr_3 followed by intramolecular ester exchange reaction afforded the chromeno[*3,4-c*]pyrrol derivative **6h** in 61% yield (Fig. 3).

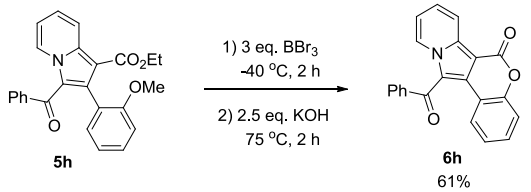


Fig 3 Synthesis of polycyclic compound **6h**.

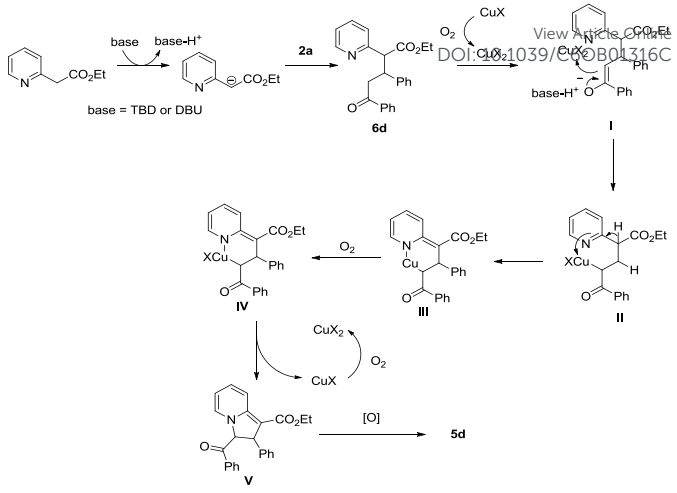


Fig. 4 The proposed mechanism.

To confirm the proposed mechanism (Fig. 2), the reaction was carried out in two steps. We found that nearly quantitative Michael addition product **6d** was formed in the existence of DBU or TBD after 20 min at room temperature. And C-N coupling procedure happened with 59% yield under CuCl/TBD system and 69% yield under $Cu(OAc)_2$/DBU system (See SI). Although the mechanistic details are unclear at the present time, a probable mechanism is shown in Fig. 4. DBU or TBD[21] activated ethyl 2-(pyridin-2-yl)acetate to give the Michael addition product **6d**, which was also activated by base to form **I**. Then **I** reacted with Cu(II) to produce the intermediate **III** that is then oxidized to the reactive copper complex **IV**.[25] Afterwards, **IV** afforded the product **V** through reductive elimination along with Cu(I) species which is oxidized by the aerobic oxygen to enter the catalytic cycle. Finally, **5d** was formed by oxidative aromatization.[26]

Conclusions

We have disclosed an efficient aerobic copper-catalyzed [3+2] cycloaddition for a "one-pot" synthesis of pyrrolo[1,2-a]quinolines, pyrrolo[2,1-a]isoquinolines and indolizines. This procedure was involved tandem Michael addition, C-N coupling and annulation. Moreover, a procedure by demethylation of the methoxy group and intramolecular ester exchange to obtain polycyclic coumarin compound in moderate yield.

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