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# One-Pot Synthesis of Pyrrolo[1,2-*a*]quinoxaline Derivatives via a Copper-Catalyzed Aerobic Oxidative Domino Reaction

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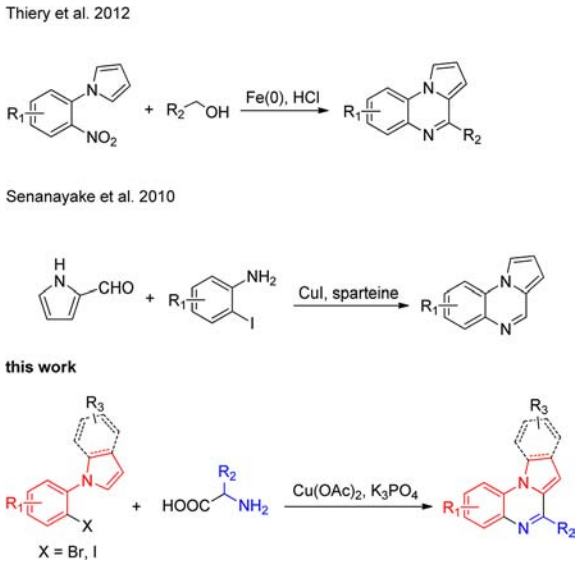
Supporting Information

**ABSTRACT:** A copper-catalyzed process for the synthesis of pyrrolo[1,2-*a*]quinoxalines from readily available α-amino acids and 1-(2-halophenyl)-1*H*-pyrroles is described. Different functional groups were well tolerated to give the corresponding products.


The pyrrolo[1,2-*a*]quinoxaline skeleton is present in various biologically active agents and plays an important role in medicinal chemistry. For example, some substituted (phenylamino) pyrrolo[1,2-*a*]quinoxaline-carboxylic acid derivatives promised utilization for a novel class of potent inhibitors of the human protein kinase CK2.[1] Some 5,6-dihydro-indolo[1,2-*a*]quinoxalines exhibit antifungal activities in vitro against the phytopathogenic fungi and revealed their potential role as novel promising lead candidates for further design and synthesis of agricultural fungicides.[2] 2-(Aminomethyl)-4-phenylpyrrolo[1,2-*a*]-quinoxalines have been found to possess a central dopamine antagonist activity.[3] Furthermore, many derivatives have been proven to possess other biological activities, including in vitro antiparasitic activities,[4] potential nonpeptide glucagon receptor antagonist activities,[5] 5-$HT_3$ receptors,[6] antiproliferative activity,[7] and antimycobacterial agents.[8] In addition, some of them are also used as fluorescent probes for amyloid fibril.[9]

Due to their great value, the preparation of pyrrolo[1,2-*a*]quinoxalines has gained much attention.[10] Unsubstituted pyrrolo[1,2-*a*]quinoxalines were first synthesized from 2-(1*H*-pyrrol-1-yl)anilines and $HCO_2H$ by Cheeseman and Tuck in 1965.[11] Two other traditional strategies have been followed. One synthetic method utilized acyl chlorides with 2-(1*H*-pyrrol-1-yl)anilines to access the acetamides, followed by reaction with $POCl_3$ to obtain the pyrrolo[1,2-*a*]quinoxalines according to the Bischler−Napieralski reaction.[12] The other method involves the reaction between 2-(1*H*-pyrrol-1-yl)-anilines and aldehydes to obtain the intermediates, followed by an oxidation process to give the target compounds.[13] In those cases, volatile and toxic reagents such as aldehydes were used, and multistep syntheses led to low atom economy. Recently, the Thiery group reported an Fe(0)-catalyzed strategy from nitroarenes and alcohols to assemble these compounds,[14] but this strategy needs excessive Fe catalyst and volatile HCl (Scheme 1). The Senanayake group developed a Cu-catalyzed strategy from 2-formylpyrroles and *o*-amino-iodoarenes to construct pyrrolo[1,2-*a*]quinoxalines,[15] but this method involved an expensive ligand. Therefore, it is highly desirable to develop an efficient, minimally toxic, and convenient approach for the synthesis of those heterocycles.

**Scheme 1. Different protocols for the syntheses of pyrrolo[1,2-*a*] quinoxalines**




Recently, copper-catalyzed Ullmann coupling reactions have made significant progress, and many *N*-heterocycles have been synthesized by us[16] and other groups.[17] However, most of the reactions were performed under a nitrogen or argon atmosphere. In addition, most of the cyclization reactions which occurred at the C-2 position of pyrroles or indoles require acid to activate the pyrrole ring system. Furthermore, reports regarding Cu-catalyzed construction of pyrrolo[1,2-*a*]quinoxalines are still rare. Herein, we report an efficient,

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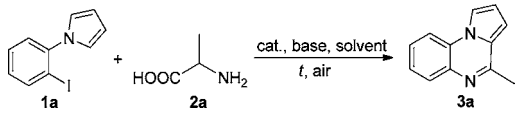
minimally toxic, and convenient Cu-catalyzed one-pot domino reaction of α-amino acids and 1-(2-halophenyl)-1*H*-pyrroles for the synthesis of pyrrolo[1,2-*a*]quinoxalines in air.

To identify the best reaction conditions, 1-(2-iodophenyl)-1*H*-pyrrole (**1a**) and alanine (**2a**) were initially used as the model substrates under different conditions (Table 1). The

**Table 1. Optimization of Reaction Conditions**[a]




1a 2a 3a

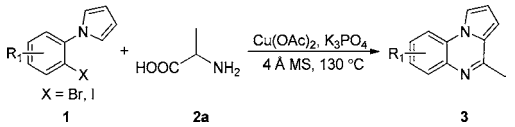
| entry | cat. | base | solvent | *t*, °C | yield, %[b] |
|---|---|---|---|---|---|
| 1 | CuBr | $K_2CO_3$ | DMSO | 130 | 32 |
| 2 | CuI | $K_2CO_3$ | DMSO | 130 | 13 |
| 3 | CuCl | $K_2CO_3$ | DMSO | 130 | 15 |
| 4 | $Cu(OAc)_2$ | $K_2CO_3$ | DMSO | 130 | 52 |
| 5 | $CuCl_2·2H_2O$ | $K_2CO_3$ | DMSO | 130 | trace |
| 6 | $CuBr_2$ | $K_2CO_3$ | DMSO | 130 | trace |
| 7 | $CuSO_4·5H_2O$ | $K_2CO_3$ | DMSO | 130 | trace |
| 8 | $Cu(CF_3SO_3)_2$ | $K_2CO_3$ | DMSO | 130 | 46 |
| 9 | – | $K_2CO_3$ | DMSO | 130 | 0 |
| 10 | $Cu(OAc)_2$ | KTB | DMSO | 130 | trace |
| 11 | $Cu(OAc)_2$ | $K_3PO_4$ | DMSO | 130 | 56 |
| 12 | $Cu(OAc)_2$ | NaOH | DMSO | 130 | 16 |
| 13 | $Cu(OAc)_2$ | $Cs_2CO_3$ | DMSO | 130 | 48 |
| 14 | $Cu(OAc)_2$ | $K_3PO_4$ | NMP | 130 | 12 |
| 15 | $Cu(OAc)_2$ | $K_3PO_4$ | DMF | 130 | 49 |
| 16 | $Cu(OAc)_2$ | $K_3PO_4$ | dioxane | 130 | trace |
| 17 | $Cu(OAc)_2$ | $K_3PO_4$ | PhCl | 130 | 0 |
| 18 | $Cu(OAc)_2$ | $K_3PO_4$ | DMSO | 150 | 37 |
| 19 | $Cu(OAc)_2$ | $K_3PO_4$ | DMSO | 110 | 16 |
| 20 | $Cu(OAc)_2$ | $K_3PO_4$ | DMSO | 130 | 67[c] |
| 21 | $Cu(OAc)_2$ | $K_3PO_4$ | DMSO | 130 | trace[d] |

[a]Reaction conditions: 1-(2-iodophenyl)-1*H*-pyrrole (**1a**) (0.3 mmol), 2-aminoacetic acid (**2a**) (1.2 mmol), catalyst (0.06 mmol), base (1.5 mmol), solvent (3 mL), under air, 3 h. [b]Isolated yield. [c]Reaction with 4 Å molecular sieves (4 Å MS). [d]Reaction was performed under nitrogen.

efficiency of different Cu catalysts was tested using $K_2CO_3$ as the base in DMSO under air at 130 °C (entries 1−8). We found that the copper salts have a remarkable impact on the reaction yield, and $Cu(OAc)_2$ gave the best yield. Reaction without a catalyst was also explored with no corresponding product observed (entry 9). Different bases were screened (entries 4 and 10−13), and $K_3PO_4$ showed the best activity. Subsequently, the evaluation of solvents reveals that DMSO was superior to NMP, DMF, dioxane, and PhCl (entries 11 and 14−17). Only 37% and 16% isolated yields were obtained when the reaction temperature was varied (entries 18 and 19). The yield was further improved by using 4 Å molecular sieves (entry 20). Finally, we attempted the reaction under a $N_2$ atmosphere (entry 21), and only a trace amount of product was observed.

Under the optimal conditions, the scope of 1-(2-halophenyl)-1*H*-pyrroles was investigated. As shown in Table 2, most of the tested substrates provided moderate to good yields. Reactions with 1-(2-halophenyl)-1*H*-pyrroles containing electron-withdrawing groups proceeded smoothly to give the target products (entries 3−9). Other representatives with electron-neutral (H) and electron-donating (4-Me) groups were also found to be suitable for this transformation, although

**Table 2. Preparation of Compounds 3a−i**[a]




1 2a 3

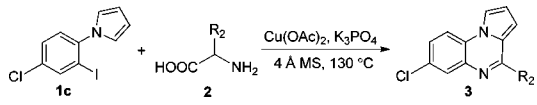
| entry | 1 | 3 | yield, %[b] |
|---|---|---|---|
| 1 | $R_1$ = H, X = I, **1a** | **3a** | 67 |
| 2 | $R_1$ = H, X = Br, **1b** | **3a** | 54 |
| 3 | $R_1$ = 4-Cl, X = I, **1c** | **3b** | 78 |
| 4 | $R_1$ = 4-$CF_3$, X = I, **1d** | **3c** | 81 |
| 5 | $R_1$ = 4-F, X = I, **1e** | **3d** | 71 |
| 6 | $R_1$ = 4-CN, X = I, **1f** | **3e** | 78 |
| 7 | $R_1$ = 4-$OCF_3$, X = Br, **1g** | **3f** | 83 |
| 8 | $R_1$ = 5-F, X = Br, **1h** | **3g** | 59 |
| 9 | $R_1$ = 5-Cl, X = Br, **1i** | **3h** | 62 |
| 10 | $R_1$ = 4-Me, X = I, **1j** | **3i** | 47 |
| 11 | $R_1$ = 4-Me, X = Br, **1k** | **3i** | 38 |

[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.2 mmol), $Cu(OAc)_2$ (0.06 mmol), $K_3PO_4$ (1.5 mmol), DMSO (3 mL), 4 Å MS, under air, 3 h. [b]Isolated yield.

the yields were lower (entries 1, 2, 10, and 11). It is worth mentioning that the substrates bearing an iodine group had higher reactivity than those bearing a bromide group (entries 1, 2, 10, and 11).

Encouraged by these promising results, we further investigated substituted α-amino acids as shown in Table 3.

**Table 3. Preparation of Compounds 3j−p**[a]




1c 2 3

| entry | 2 | 3 | yield, %[b] |
|---|---|---|---|
| 1 | $R_2$ = Me, **2a** | **3b** | 78 |
| 2 | $R_2$ = H, **2b** | **3j** | 72 |
| 3 | $R_2$ = Et, **2c** | **3k** | 75 |
| 4 | $R_2$ = Pr, **2d** | **3l** | 69 |
| 5 | $R_2$ = *i*-Pr, **2e** | **3m** | 46 |
| 6 | $R_2$ = *i*-Bu, **2f** | **3n** | 67 |
| 7 | $R_2$ = Cy, **2g** | **3o** | 35 |
| 8 | $R_2$ = Ph, **2h** | **3p** | 12 |

[a]Reaction conditions: **1c** (0.3 mmol), **2** (1.2 mmol), $Cu(OAc)_2$ (0.06 mmol), $K_3PO_4$ (1.5 mmol), DMSO (3 mL), 4 Å MS, under air, 3 h. [b]Isolated yield.

Diverse α-amino acids that underwent the reaction with 1-(4-chloro-2-iodophenyl)-1*H*-pyrrole **1c** worked well to give the corresponding products. Notably, the α-amino acids with a Cy group and a Ph group showed lower reactivity, with only 35% and 12% yields, respectively. Conversion rates of the raw materials are low. One possible reason is that the steric hindrance caused by the $R_2$ group made the pyrrole ring system less reactive.

To expand the applicability of this method, we next examined the substituted 1-(2-halophenyl)-1*H*-indoles as shown in Table 4. Different functional groups at different positions of **1l−1q** were tolerated in the reaction to afford the target products in 48% to 84% yields. Moreover, the attachments of a 3-Me group to the indole ring afford a higher yield than those without it (entries 1−4). It is obvious that the



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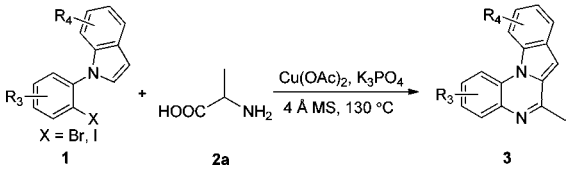
**Table 4. Preparation of Compounds 3q−t[a]**



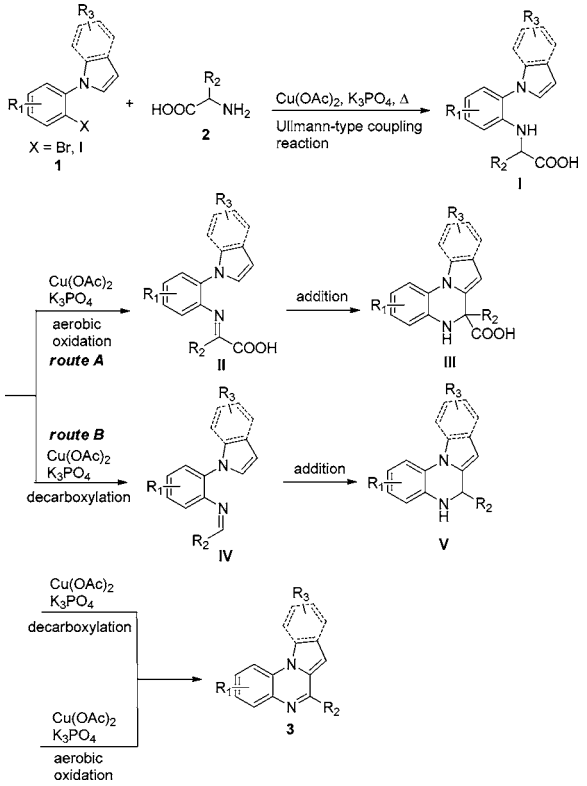

| entry | 1 | 3 | yield, %[b] |
|---|---|---|---|
| 1 | $R_3$ = H, $R_4$ = H, X = I, **1l** | **3q** | 74 |
| 2 | $R_3$ = H, $R_4$ = H, X = Br, **1m** | **3q** | 63 |
| 3 | $R_3$ = H, $R_4$ = 3-Me, X = I, **1n** | **3r** | 84 |
| 4 | $R_3$ = H, $R_4$ = 3-Me, X = Br, **1o** | **3r** | 65 |
| 5 | $R_3$ = H, $R_4$ = 6-Cl, X = I, **1p** | **3s** | 56 |
| 6 | $R_3$ = 4-Me, $R_4$ = H, X = Br, **1q** | **3t** | 48 |

[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.2 mmol), $Cu(OAc)_2$ (0.06 mmol), $K_3PO_4$ (1.5 mmol), DMSO (3 mL), 4 Å MS, under air, 3 h. [b]Isolated yield.

3-Me group increased the nucleophilicity of the ring system, which facilitates intramolecular attack of the C-2 position of the indole to afford the cyclized products.

An assumed pathway for the formation of pyrrolo[1,2-*a*]quinoxaline derivatives is illustrated in Scheme 2 according to

**Scheme 2. Proposed Reaction Mechanism**




the results above and previous research.[18] First, the Cu-catalyzed Ullmann-type coupling reaction occurs between substrates **1** and **2** to afford intermediate **I**. Next, **I** can undergo two pathways (route A and route B). Through route A, aerobic oxidation of **I** leads to **II**, then intramolecular addition of **II** affords **III**, and decarboxylation of **III** gives final product **3**. Through route B, decarboxylation of **I** gives **IV**. Subsequently intramolecular addition of **IV** yields **V**. Finally, aerobic oxidation of **V** provides **3**.

The UV−vis absorption and emission spectra of **3q**, **3r**, **3s**, and **3t** in highly dilute solution were collected (in ESI).

In conclusion, we have developed an efficient and convenient Cu-catalyzed one-pot domino reaction from 1-(2-halophenyl)-1*H*-pyrroles and readily available *α*-amino acids for the synthesis of pyrrolo[1,2-*a*]quinoxalines in air. The domino process includes Ullmann-type *N*-arylation, aerobic oxidation, intramolecular addition, and decarboxylation. It is interesting that the intramolecular addition step was achieved under conditions with a base rather than an acid. By further elaboration and diversification of the various functional groups, a wide range of *N*-heterocycles can be produced. This Cu-catalyzed one-pot process has potential applications in the synthesis of biologically and medicinally relevant compounds.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experiment details, spectra data, UV−vis absorption and emission spectra, and $^1H$ and $^{13}C$ NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01167.

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### Notes

The authors declare no competing financial interest.

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