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Efficient Copper-Catalyzed Annulation of 2-Formylazoles with 2-Haloanilines for the Synthesis of Pyrrole- and Imidazole-Fused Quinoxalines

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Promoted by CuI/2-hydroxybenzohydrazide catalytic system, a variety of pyrrole- and imidazole-fused quinoxalines have been efficiently one-pot synthesized from pyrrole-/imidazole-2-carboxaldehyde and 2-haloanilines in moderate to excellent yields.

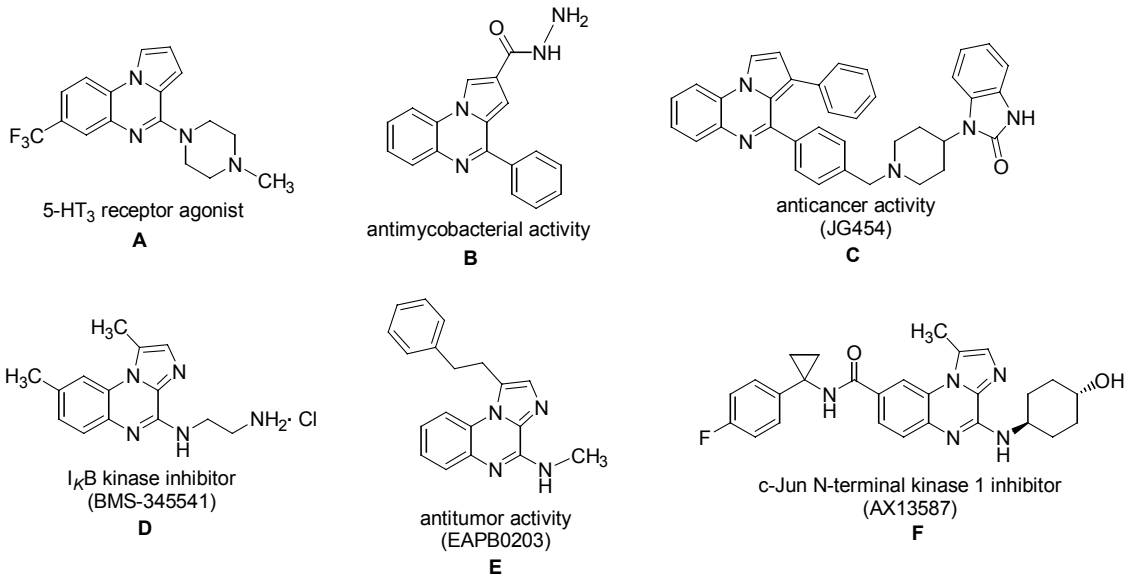
Keywords 2-haloaniline, copper, 2-hydroxybenzohydrazide, annulation, pyrrole-/imidazole-[1,2-*a*]quinoxalines

Introduction

Pyrrolo[1,2-*a*]quinoxalines[1] and imidazo[1,2-*a*]-quinoxalines[2] are important tricyclic nitrogen-containing heterocyclic compounds found in numerous pharmaceuticals and exhibit a wide range of important physiological and biological properties. These properties are important for many applications, some of which include their use as 5-HT_3 receptor agonist[1a] (Scheme 1, compound **A**), antimycobacterial agents[1b] (compounds **B**), anticancer agents[1c,2a] (compounds **C** and **E**) and kinase inhibitors[2b,2c] (compounds **D** and **F**). Consequently, the development of novel and highly efficient methods to construct these fused heterocycles is highly desirable for drug discovery.

The conventional approach for the synthesis of pyrrolo[1,2-*a*]quinoxalines has been carried out from 2-nitroaniline *via* three steps including formation of pyrrole ring, reduction of nitro group to amino and Bischler-Napieralski intramolecular cyclization,[1,3,4] and similar procedures are reported for the synthesis of imidazo[1,2-*a*]quinoxalines.[2c-2e] However, these procedures limit the scope of suitable substrates and need

Scheme 1 Biologically active pyrrolo[1,2-*a*]- and imidazo[1,2-*a*]quinoxalines and their derivatives



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multistep synthesis which lead to modest overall yields. Recently, the application of transition-metal-catalyzed strategy has been reported for these two classes of compounds synthesis.[4,5] For example, Thiéry and co-workers presented a one-pot Fe(0)-promoted method to synthesize 4,7-disubstituted pyrrolo[1,2-*a*]-quinoxalines from 1-(2-nitrophenyl)pyrroles and alphatic or benzylic alcohols.[4] Ma *et al.* reported a copper-catalyzed domino process for benzo[4,5]imidazo[1,2-*a*]quinoxalines synthesis.[5a] Reeves *et al.* and Biswas *et al.* reported, respectively, that using copper/ligand catalytic systems, the annulation of 2-formylazoles with 2-haloaniline took place efficiently to form pyrrolo[1,2-*a*]quinoxalines[5b] and isoindolo[2,1-*a*]quinoxalines[5c]. Maes *et al.* developed a Pd-catalyzed amination of 2-chloro-3-iodopyridine and 2,3-dibromopyridine with benzodiazinamines to yield imidazo[1,2-*a*]quinoxalines.[5d] The aforementioned cases overcome the drawbacks of the traditional methods, and achieved one-pot synthesis for these compounds. Notably, the ligands in these transition-metal catalytic systems play an important role in the annulation of 2-formylazoles with 2-haloanilines.

Previously, we have demonstrated several typical ligand-assisted copper-catalyzed Ullmann-type *N*-arylation of nitrogen-containing heterocycles with aryl halides in organic solvent[6] or aqueous media.[7] As an extension, we herein report CuI/2-hydroxybenzohydrazide[7a] as an efficient catalytic system for cascade reaction between pyrrole-/imidazole-2-carboxaldehyde and 2-haloanilines to construct pyrrolo-/imidazo[1,2-*a*]-quinoxalines.

Experimental

General

Unless otherwise stated, all reagents were purchased from *Adamas*-beta and used without further purification. Column chromatography was performed with silica gel (200－300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography was carried out with Merck silica gel GF_{254} plates. All cyclization products are characterized by ^{1}H NMR and GC-MS, which were compared with the previously reported dates. ^{1}H NMR spectra were recorded at room temperature on a Varian Inova-400 instrument at 400 MHz for ^{1}H NMR. Mass spectra were recorded on Agilent 7890A/5975C (GC-MS, EI model) or Agilent G6530 Q-TOF (HRMS, ESI model) instrument.

General procedure for the synthesis of pyrrole- and imidazole-fused quinoxalines

To a 10 mL of sealed tube was added CuI (0.025 mmol), **L3** (0.05 mmol), pyrrole- or imidazole-2-carboxaldehyde (0.5 mmol), 2-iodoaniline (0.75 mmol), Cs_2CO_3 (1.0 mmol) and DMF (1 mL). The reaction mixture was reacted at 120 ℃ in a preheated oil bath for 24 h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (20 mL×3). The combined organic phases was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether as the eluent) to afford the target product.

Results and Discussion

Initially, pyrrole-2-carboxaldehyde and 2-iodoaniline were chosen as the model substrate to optimize the reaction conditions, including copper sources, ligands, bases and solvents. The results are listed in Table 1. Inverstigation into the ligand revealed that the reaction proceeded smoothly with 71% yield when the reaction was carried out using a combination of CuI (10 mol%), **L3** (20 mol%), K_3PO_4 (2 equiv.) in DMF at 120 ℃ for 12 h (Entry 3). Methylation of hydroxyl (**L4**) or non-amide nitrogen atom (**L5**) of 2-hydroxybenzohydrazide results in a slight decrease yields (Entries 4 and 5). To our surprise, moderate yields were also obtained when **L1** or **L2**, two common commercial chemicals, were employed as the assisting ligands (Entries 1 and 2). Control experiments were carried out to reveal that 38% yield was obtained without any ligand and no product observed in the absence of copper catalyst (Entries 6 and 7). Among the copper sources screened, CuI proved to be the best choice (Entries 8－11). Several bases were assayed, and Cs_2CO_3 provided the highest yield (Entries 12－14). It is noteworthy that decreasing the catalyst loading from 10 mol% to 5 mol% did not lead to a decrease of yield, and 74% yield was also afforded (Entry 15). However, a further reducing of CuI loading to 2.5 mol% results in lower yield (Entry 16). In different solvents other than DMF, efficiencies of the reactions were decreased significantly (Entries 17－20). Finally, we were pleased to find that 92% yield was obtained with prolonging the reaction time from 12 to 24 h (Entry 21). However, lowering the reaction temperature form 120 to 100 ℃ led to a dramatic decrease in the yield (Entry 22). In summary, the combination of 5 mol% CuI, 10 mol% **L3** and Cs_2CO_3 in DMF at 120 ℃ for 24 h was the optimal condition.

Under the optimal conditions, the application of the CuI/**L3** catalyst system was explored with various 2-haloanilines and pyrrole-/imidazole-2-carboxaldehyde. As shown in Table 2, the cascade reactions were performed well for most of 2-iodoanilines with electron-rich, electron-neutral and electron-poor groups to afford corresponding pyrrolo[1,2-*a*]quinoxalines in good to excellent yields (Entries 1－7). Moreover, heterocyclic aminoiodoarene could also be reacted well with 78% yield (Entry 8). Additionally, aminobromoarene provided 68% yield, while aminochloroarene afforded only trace of product under the experimental conditions (Entries 9 and 10).

As pointed out by the results displayed in Table 3, the further extension of the reaction to imidazole-2-carboxaldehyde was also successful. All the 2-iodo/

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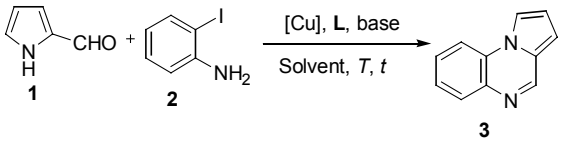
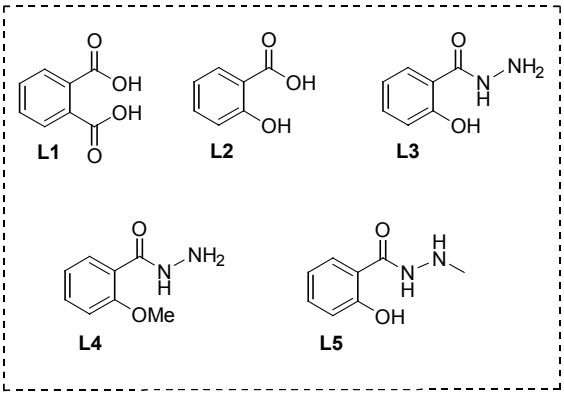
bromoanilines examined participate in cascade reactions

Table 1 Copper-catalysed annulation of pyrrole-2-carboxaldehyde with 2-iodoaniline: optimization of conditions[a]

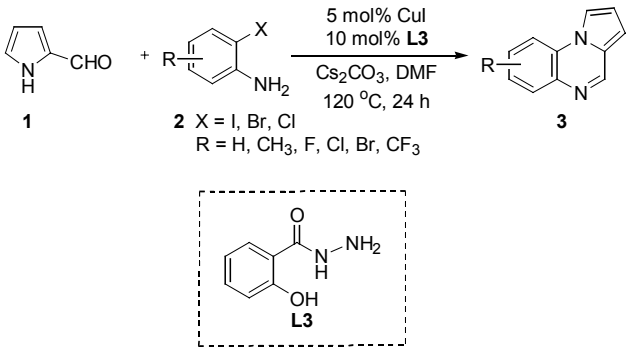


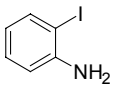
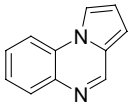
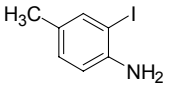
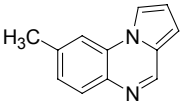
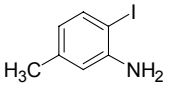
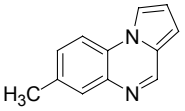
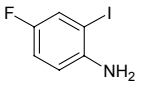
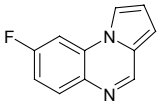
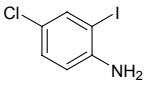
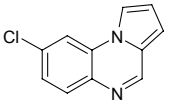
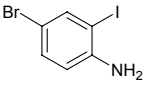
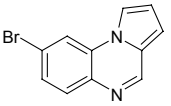
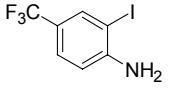
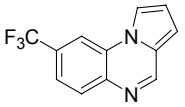
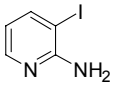
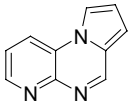
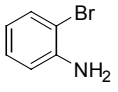
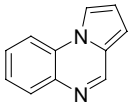
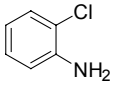
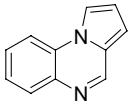


Entry	[Cu]	Ligand	Base	Solvent	*T*/℃	Yield[b]/%
1	CuI	**L1**	K_3PO_4	DMF	120	61
2	CuI	**L2**	K_3PO_4	DMF	120	55
3	CuI	**L3**	K_3PO_4	DMF	120	71
4	CuI	**L4**	K_3PO_4	DMF	120	62
5	CuI	**L5**	K_3PO_4	DMF	120	53
6	CuI	—	K_3PO_4	DMF	120	38
7	—	**L3**	K_3PO_4	DMF	120	0
8	CuO	**L3**	K_3PO_4	DMF	120	46
9	$CuSO_4$	**L3**	K_3PO_4	DMF	120	58
10	Cu_2O	**L3**	K_3PO_4	DMF	120	56
11	CuBr	**L3**	K_3PO_4	DMF	120	68
12	CuI	**L3**	Na_2CO_3	DMF	120	14
13	CuI	**L3**	K_2CO_3	DMF	120	34
14	CuI	**L3**	Cs_2CO_3	DMF	120	75
15	CuI	**L3**	Cs_2CO_3	DMF	120	74[c]
16	CuI	**L3**	Cs_2CO_3	DMF	120	55[d]
17	CuI	**L3**	Cs_2CO_3	DMSO	120	57[c]
18	CuI	**L3**	Cs_2CO_3	DMAC	120	42[c]
19	CuI	**L3**	Cs_2CO_3	Dioxane	120	6[c]
20	CuI	**L3**	Cs_2CO_3	Toluene	120	15[c]
21	CuI	**L3**	Cs_2CO_3	DMF	120	92[c,e]
22	CuI	**L3**	Cs_2CO_3	DMF	100	40[c]

[a] Reaction conditions: pyrrole-2-carboxaldehyde (0.5 mmol), 2-iodoaniline (0.75 mmol), [Cu] (0.05 mmol), ligand (0.1 mmol), base (1.0 mmol), solvent (1 mL), 120 ℃, 12 h. [b] Isolated yield. [c] CuI (0.025 mmol), **L3** (0.05 mmol). [d] CuI (0.0125 mmol), **L3** (0.025 mmol). [e] Reaction time: 24 h.

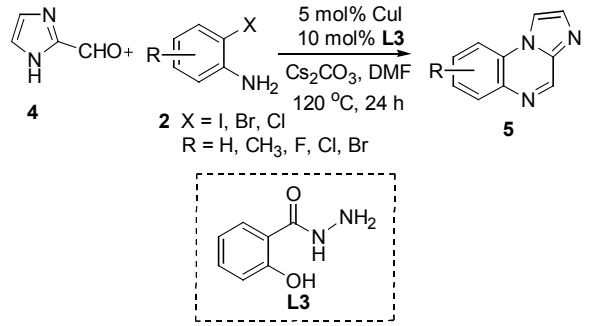
Table 2 CuI/**L3** catalyzed annulation of pyrrole-2-carboxaldehyde with substituted 2-haloaniline[a]

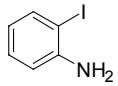
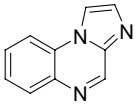
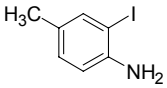
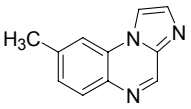
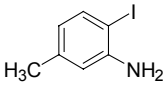
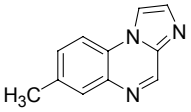
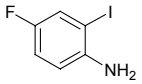
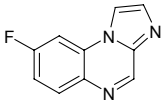
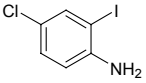
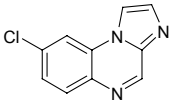
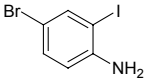
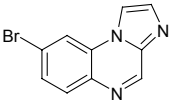
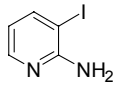
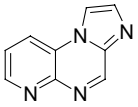
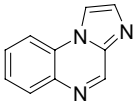
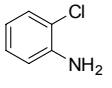
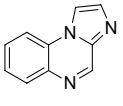


Entry	2-Haloaniline	Product	**3**	Yield[b]/%
1			**3a**	92
2			**3b**	80
3			**3c**	73
4			**3d**	64
5			**3e**	84
6			**3f**	80
7			**3g**	64
8			**3h**	78
9			**3a**	68
10			**3a**	trace

[a] Reaction conditions: pyrrole-2-carboxaldehyde (0.5 mmol), 2-iodoaniline (0.75 mmol), CuI (0.025 mmol), **L3** (0.05 mmol), Cs_2CO_3 (1.0 mmol), DMF (1 mL), 120 ℃, 24 h. [b] Isolated yield.

Table 3 CuI/**L3** catalyzed annulation of imidazole-2-carboxaldehyde with substituted 2-haloaniline[a]



Entry	2-Haloaniline	Product	5	Yield[b]/%
1			**5a**	68
2			**5b**	56
3			**5c**	63
4			**5d**	65
5			**5e**	68
6			**5f**	55
7			**5g**	40
8			**5a**	62
9			**5a**	trace

[a] Reaction conditions: imidazole-2-carboxaldehyde (0.5 mmol), 2-iodoaniline (0.75 mmol), CuI (0.025 mmol), **L3** (0.05 mmol), Cs_2CO_3 (1.0 mmol), DMF (1 mL), 120 ℃, 24 h. [b] Isolated yield.

with imidazole-2-carboxaldehyde that occur in moderate to good yields (Entries 1—8). Unfortunately, the annulation of imidazole-2-carboxaldehyde with 2-chloroaniline under these conditions was still a challenge (Entry 9).

Conclusions

In conclusion, we have established a simple one-pot copper-catalyzed method allowing the direct synthesis of various of pyrrolo[1,2-*a*]- and imidazo[1,2-*a*]quinoxalines from substituted 2-haloanilines with pyrrole- and imidazole-2-carboxaldehyde in moderate to excellent yields by using 2-hydroxybenzohydrazide as an idea ligand. The low catalyst loading, stable and easy-synthesis of ligand, experimental simplicity and without inert atmosphere are the features of the catalytic process presented in the current paper.

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