RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2019, **9**, 13414

Copper-catalyzed synthesis of 2-aminopyridylbenzoxazoles *via* domino reactions of intermolecular *N*-arylation and intramolecular *O*-arylation†

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Received 13th March 2019
Accepted 25th April 2019

DOI: 10.1039/c9ra01908a

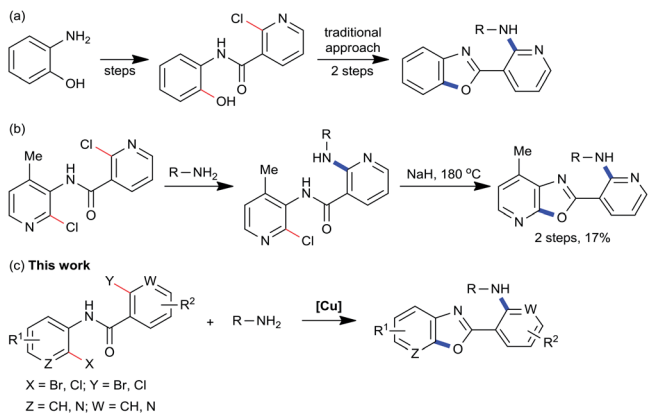
rsc.li/rsc-advances

A simple and general approach to nitrogen-containing heterocycles *via* copper-catalyzed domino reaction has been developed, and the corresponding 2-aminopyridylbenzoxazole derivatives were obtained in good to excellent yields using the readily available starting materials. This method possesses unique step economy features, and is of high tolerance towards various functional groups in the substrates.

Introduction

Nitrogen-containing heterocycles are ubiquitous subunits of a variety of biologically active substances,[1] and they have been assigned as privileged structures in drug discovery.[2] The 2-aminopyridylbenzoxazole derivatives have attracted much attention for their wide applications as enzyme inhibitors,[3] activators,[4] and fluorescence sensors.[5] The development of new methods and strategies for the direct formation of several C-heteroatom bonds is an ongoing subject for organic chemists. The C-heteroatom reaction has played a prominent role in this context due to its suitability for complex structure formation, and featured in dozens of syntheses.[6] Despite many attempts to improve the efficiency and practicality of the synthesis of benzoxazoles, the majority of conditions still require stepwise formation (such as 4 steps),[3a] and use extra additives (such as polyphosphoric acid),[3b] or elevated temperature.[4] Additionally, it is commonplace that costly 2-aminophenol substrates are required to access the 2-halo-*N*-(2-hydroxyphenyl)nicotinamides employed in these procedures (Scheme 1a).[4] Another approach to benzoxazole derivatives involves the oxidative cyclization of bisaryloxime ethers.[7] Herein, a simple method is disclosed wherein domino reactions of readily available 2-halo-*N*-(2-haloaryl)nicotinamides with amines are performed well under mild conditions.

Copper-catalyzed domino reactions, through the incorporation of several distinct transformations into one single sequence, are one of the most powerful synthetic tools in modern organic chemistry.[8] Their application to the construction of *N*-heterocycles has been reported by us[9] and other research groups.[10] Recently, research efforts in this laboratory have explored the utility of 2-halo-*N*-(2-halophenyl)benzamide and 2-(2-halophenyl)benzoimidazole derivatives as starting materials in a variety of domino C-heteroatom reactions, including C–C/C–N formation,[11] C–N/C–N formation,[12] and C–C/C–N/C–N formation.[13] The success of these domino processes prompted the investigation of amines as suitable reagents towards forging C–N/C–O bonds. The development of such a reaction was motivated by several useful amines that are extremely laborious to access.[14] An illustrative example is depicted in Scheme 1b, wherein an 2-aminopyridylbenzoxazole derivative was accessed from a 2-halo-*N*-(2-haloaryl)nicotinamide in two steps.[15] Unfortunately, the 2-aminopyridylbenzoxazole product was isolated in only 17% yield. In contrast, a mild domino C-heteroatom strategy could dramatically simplify the pathway to 2-aminopyridylbenzoxazoles because the *in situ* nicotinamide group could be viewed as a directing group for C–N formation. This method would provide convenient access to 2-aminopyridylbenzoxazole derivatives without addition of any ligands or additives (Scheme 1c).



Scheme 1 Methods for the synthesis of 2-aminopyridylbenzoxazoles.

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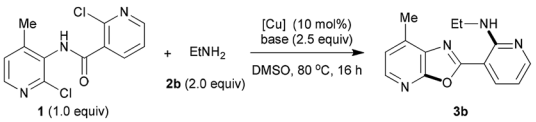
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra01908a

Results and discussion

As shown in Table 1, 2-chloro-*N*-(2-chloro-4-methylpyridin-3-yl) nicotinamide (**1**) and ethanamine (**2b**) were chosen as the model substrates to optimize reaction conditions including catalysts, and bases under nitrogen atmosphere. Compound **1** was prepared from *ortho*-haloarylamines and acyl chlorides.[16] Previously, we demonstrated that a combination of weak coordination from the heteroatom directing group of the substrate on the Cu centre could accelerate C(sp^2)–X activation.[11–13] We therefore began screening of copper catalysts in the presence of 2.5 equiv. of K_2CO_3 as base, and DMSO as solvent at 80 °C. To our delight, when we introduced copper powder into the reaction mixture, we obtained the desired reaction product in 40% yield (entry 1). Further screening of copper catalysts revealed that Cu(I) gave a higher yield (entries 2–9). For example, the $CuCl_2$ gave a yield of 63%, but the CuCl improved the yields to 72%. In normal copper(I) promoted reactions, the ease of introduction of a halogen from the copper salts follows the order Cl > Br > I. CuI provided the highest yield because of the reduced possibility of the iodide anion interfering with the desired reaction.[17] The control experiment carried out in the absence of a copper catalyst gave no target product (entry 10). Encouraged by these results, we proceeded to optimize the reaction conditions using CuI as catalyst, and found that the use of mild bases, such as potassium salts, was crucial to the reactivity. In general, the usefulness of bases may be attributed to their good solubility and ionization ability in organic solvents.[18] Among the bases screened, carbonates were found to be optimal, with 2.5 equiv. K_2CO_3 affording the highest yield of 82% (compare entries 4, 11–13). Further comprehensive screening data are presented in the ESI.†

Table 1 Optimization of the reaction conditions[a]



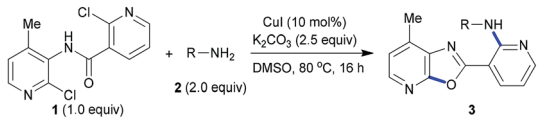
Entry	[Cu]	Base	Yield[b] (%)
1	Cu	K_2CO_3	40
2	CuCl	K_2CO_3	72
3	CuBr	K_2CO_3	75
4	**CuI**	**K_2CO_3**	**82**
5	Cu_2O	K_2CO_3	65[c]
6	$CuCl_2$	K_2CO_3	63
7	CuO	K_2CO_3	60
8	$CuSO_4$	K_2CO_3	54
9	$Cu(OAc)_2$	K_2CO_3	65
10	—	K_2CO_3	0[d]
11	CuI	Na_2CO_3	54
12	CuI	Cs_2CO_3	38
13	CuI	K_3PO_4	46

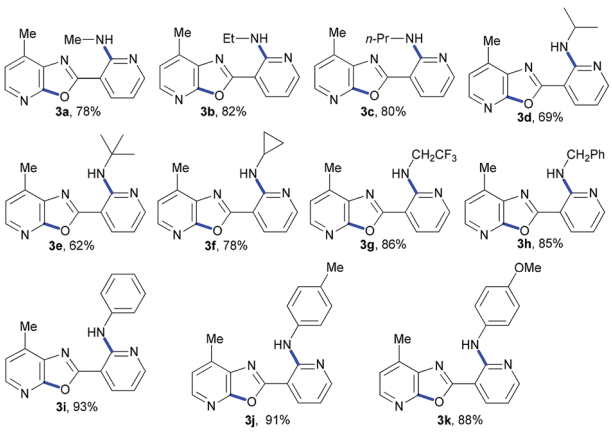
[a] Reaction condition: **1** (0.5 mmol), **2b** (1 mmol), catalyst (0.05 mmol), base (1.25 mmol), DMSO (2 mL), 80 °C, 16 h in a Schlenk tube under nitrogen atmosphere. [b] Isolated yield. [c] Cu_2O (0.025 mmol). [d] In the absence of catalyst. DMSO = dimethylsulfoxide.

Under optimal conditions, we examined the scope of copper-catalyzed domino C-heteroatom reaction of 2-chloro-*N*-(2-chloro-4-methylpyridin-3-yl)nicotinamide (**1**) with amines (**2**). As shown in Table 2, the tested substrates afforded good to excellent yields. The domino C-heteroatom reactions did not need addition of any additional ligand and additive which exhibited *ortho*-substituent effect of amide group in **1** during *N*-arylation. In the previous copper-catalyzed reactions, aryl chlorides were weak substrates, and the results also showed the *ortho*-substituent effect. A variety of amines were tested, aliphatic and aromatic amines all gave good yields. In general, the electronic properties of amines did not have much influence on the reaction, as both electron-donating and electron-withdrawing groups were well tolerated. As expected, the electron deficient 2,2,2-trifluoroethanamine underwent domino C-heteroatom reaction giving good isolated yield (**3g**). Notably, the presence of MeO substituent in products (**3k**) allows for further functionalization of the aromatic ring. A challenging problem in this domino C-heteroatom processes is the combination of **1** with sterically hindered amine substrates. To our delight, the domino reaction with isopropylamine proceeded smoothly and product **3d** was obtained in moderate yield. Remarkably, the highly hindered *tert*-butylamine could be coupled under these optimal conditions affording the corresponding product **3e** in 62% yield. In addition, the high-strain molecule cyclopropylamine was also proved to be suitable substrate, indicating a broad scope of amines.

We next extended the scope of 2-halo-*N*-(2-haloaryl)nicotinamide substrates under the standard conditions. Interestingly, *N*-(2-bromophenyl)-2-chloronicotinamide (**4**) (Table 3) and 2-

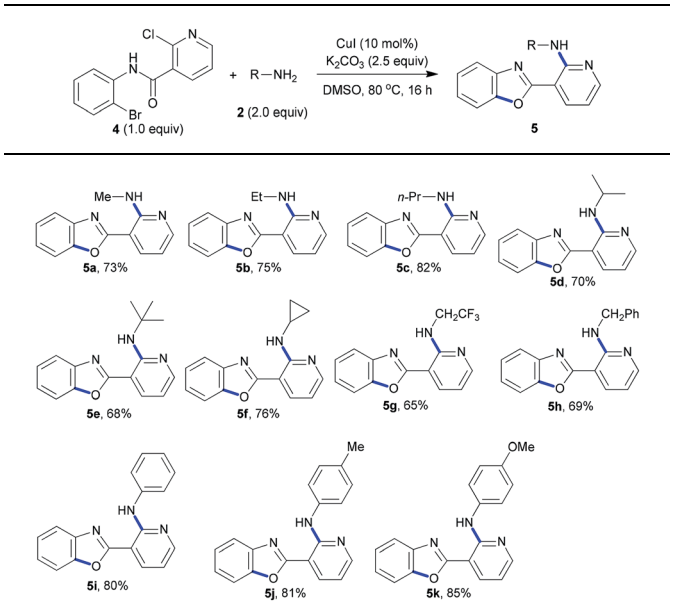
Table 2 Cu-catalyzed domino reactions of 2-chloro-*N*-(2-chloro-4-methylpyridin-3-yl)nicotinamide[a,b]





[a] Reaction condition: **1** (0.5 mmol), **2** (1 mmol), CuI (0.05 mmol), K_2CO_3 (1.25 mmol for free amines; 1.75 mmol for amine hydrogen chlorides), DMSO (2 mL), reaction temperature (80 °C) in a Schlenk tube under nitrogen atmosphere. Reaction time (16 h). [b] Isolated yield.

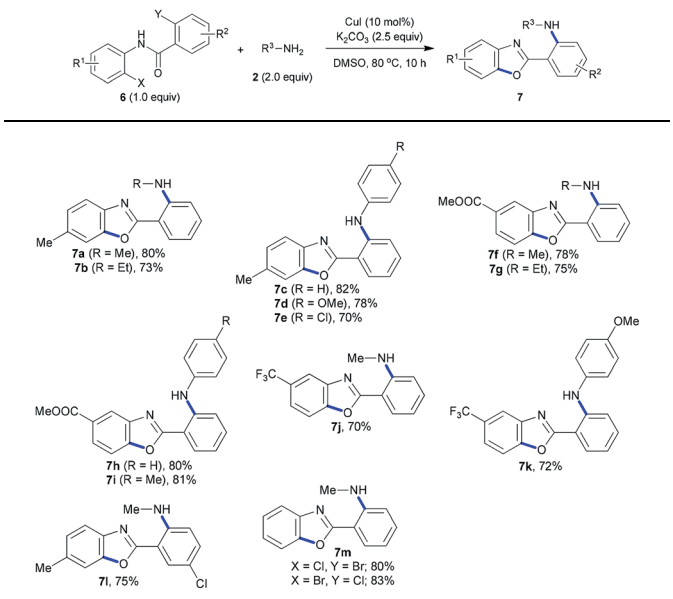
Table 3 Cu-catalyzed domino reactions of *N*-(2-bromophenyl)-2-chloronicotinamide[a,b]



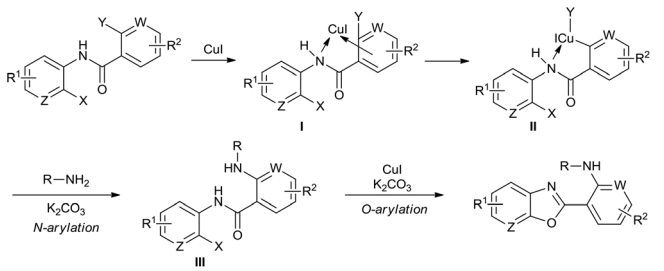
[a] Reaction condition: **4** (0.5 mmol), **2** (1 mmol), CuI (0.05 mmol), K_2CO_3 (1.25 mmol for free amines; 1.75 mmol for amine hydrogen chlorides), DMSO (2 mL), reaction temperature (80 °C) in a Schlenk tube under nitrogen atmosphere. Reaction time (16 h). [b] Isolated yield.

halo-*N*-(2-halophenyl)benzamide (**6**) (Table 4) also proceeded smoothly, and various 2-aminopyridylbenzoxazoles were synthesized in good to excellent yields. The results showed that

Table 4 Cu-catalyzed domino reactions of 2-halo-*N*-(2-halophenyl) benzamide[a,b]



[a] Reaction condition: **6** (X = Y = Br, 0.5 mmol), **2** (1 mmol), CuI (0.05 mmol), K_2CO_3 (1.25 mmol for free amines; 1.75 mmol for amine hydrogen chlorides), DMSO (2 mL), reaction temperature (80 °C) in a Schlenk tube under nitrogen atmosphere. Reaction time (10 h). [b] Isolated yield.



Scheme 2 A possible mechanism for synthesis of 2-aminopyridylbenzoxazoles.

our method was of wide application for construction of nitrogen-containing heterocycles. The copper-catalyzed domino C-heteroatom reaction of 2-halo-*N*-(2-haloaryl)nicotinamides with amines access to 2-aminopyridylbenzoxazoles could tolerate various functional groups including ester, ether, CF_3 group, C–Cl bond, and benzyl group.

In the domino reactions above, no ligand or additive were required, and the result showed *ortho*-substituent effect of nicotinamide group.[19] Therefore, a possible mechanism for synthesis of 2-aminopyridylbenzoxazole derivatives was proposed in Scheme 2. Firstly, coordination of 2-halo-*N*-(2-haloaryl)nicotinamide with CuI gives **I**, and oxidative addition of **I** leads to **II**. Intermolecular *N*-Arylation of **II** with amine provides intermediate **III**, and the intramolecular *O*-Arylation of **III** affords the target product.

Conclusions

In conclusion, we have developed a simple and general process for 2-aminopyridylbenzoxazole derivatives *via* copper-catalyzed domino reaction. The approach possesses unique step economy features, and uses the readily available substituted 2-halo-*N*-(2-haloaryl)nicotinamides or 2-halo-*N*-(2-halophenyl) benzamides and amines as the starting materials, inexpensives CuI as the catalyst, no any ligand and additive was required, and the corresponding 2-aminopyridylbenzoxazoles were obtained in good to excellent yields. This protocol is of high tolerance towards various functional groups in the substrates. Therefore, the method will attract much attention in academic and industrial researches. Further details of the mechanism and application of this methodology is being pursued in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Scientific Research Fund Project of Hainan University (KYQD(2R)1958), National Natural Science Foundation of China (21403163) and Young Technology Stars Project in Shaanxi Province of China (2018KJXX-048) for financial support.

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