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Copper catalyzed aerobic oxidative amination of 3,4-dihydroquinoxalin-2(1H)-ones

Shuocheng Wan, Jie Wang, Congde Huo *

Gansu International Scientific and Technological Cooperation Base of Water-Retention Chemical Functional Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, China

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ABSTRACT

A copper catalyzed aerobic sp^3 C—H amination of 3,4-dihydroquinoxalin-2(1H)-ones is developed. This protocol provides a concise method to access 3-aminoquinoxalinone derivatives with good functional-group tolerances, utilizing primary and secondary aliphatic amines as nitrogen sources under mild and simple reaction conditions. It provides a practical approach to the synthesis of pharmaceutical active 3-aminoquinoxalinones.

Introduction

3,4-Dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2(1H)-ones (Scheme 1) as privileged nitrogen-heterocyclic skeletons have attracted considerable attention due to their significant bio-activities and interesting chemical properties [1,2]. In 2016, we for the first time developed an oxidative C(sp^3)–C(sp^2) bond formation reaction to deliver 3-indolated 3,4-dihydro-1,4-benzoxazin-2-ones [3]. Afterward, visible-light promoted versions of this transformation were reported by the He group [4], the Lee group [5], and the Vila group [6] respectively in 2018. And a ionic-liquid variation was developed by the Sharifi group in 2020 [7]. In 2017, we described an iron-catalyzed oxidative dehydrogenative coupling reaction of 3,4-dihydro-1,4-benzoxazin-2-ones with malonic esters or ketones to construct C(sp^3)–C(sp^3) bonds [8]. In 2019, the Vila group described a copper-catalyzed aerobic oxidative C(sp^3)–C(sp) bonds forming reaction of 3,4-dihydroquinoxalin-2(1H)-ones with terminal alkynes under visible-light irradiation [9]. In 2018, we reported a copper catalyzed oxidative phosphonation reaction of 3,4-dihydro-1,4-benzoxazin-2-ones through an oxidative Pudovik reaction [10]. In 2020, the sp^3—C—H peroxidation reaction of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2(1H)-ones was achieved by our group under catalyst-free reaction conditions [11].

3-Aminoquinoxalin-2(1H)-one structure motif has been well known as an important pharmacophore to possess various potent biological activities, which has been wildly explored for therapeutic applications. For examples, as shown in Scheme 2, compound **I** (ataquimast) is applied as a tumor necrosis factor antagonist in the treatment of chronic obstructive bronchopneumopathies [12]; Compound **II** is a PAS kinase modulator [13]; Compound **III** can be used as a calcium channel blocker [14]; as well as compound **IV** acts as a histamine-4 receptor antagonist [15].

Although we and others have developed an oxidative C—H functionalization strategy to construct new C—C, C—P and C—O bond to deliver 3-substituted 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2(1H)-ones, we are still seeking more type of chemical bond formation reaction of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2(1H)-ones. C — N bond formation reaction is one of the most fundamental pursuit in organic synthesis. Encouraged by the pharmaceutical significance of 3-aminoquinoxalinone moieties, we became interested in exploring direct C—H amination of readily available 3,4-dihydroquinoxalin-2(1H)-ones with following oxidative aromatization, which seems a straightforward pathway to construct complex 3-aminoquinoxalinones.

Herein, as a part of our research on oxidative dehydrogenative C—H functionalization reactions, we reported an efficient oxidative amination aromatization tandem reaction of 3,4-dihydroquinoxalin-2(1H)-ones with primary and secondary aliphatic amines

* Corresponding author.
E-mail address: huocongde@nwnu.edu.cn (C. Huo).

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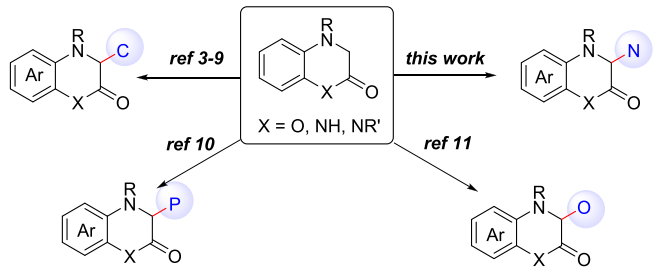
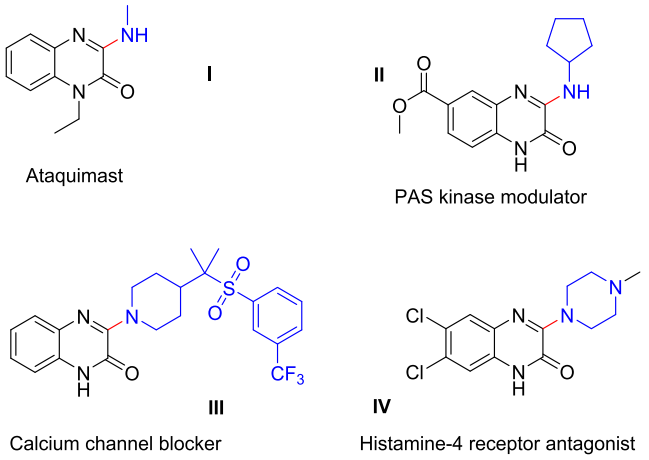


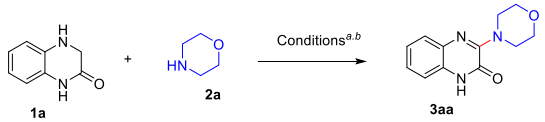
Scheme 1. C—H functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2(1H)-ones.



Scheme 2. Examples of bio-active 3-aminoquinoxalinones.

enabled by aerobic copper catalysis. A range of 3-amino substituted quinoxalin-2(1H)-ones were obtained under simple and mild reaction conditions.

Aliphatic amines are extremely valuable structural motifs in natural products and biologically active molecules. This study was initiated by investigating the reaction of 3,4-dihydroquinoxalin-2(1H)-one **1a** with morpholine **2a** in DMSO under an air atmosphere with $Cu(OAc)_2$ as the catalyst. To our delight, as shown in Scheme 3, when the mixture was heated at 60 °C for 24 h, the desired product **3aa** was isolated in 87% yield (Scheme 1, entry 1). The use of other copper salts or iron salts was found to be less effective (Scheme 3, entries 2–4). Changing the air atmosphere to

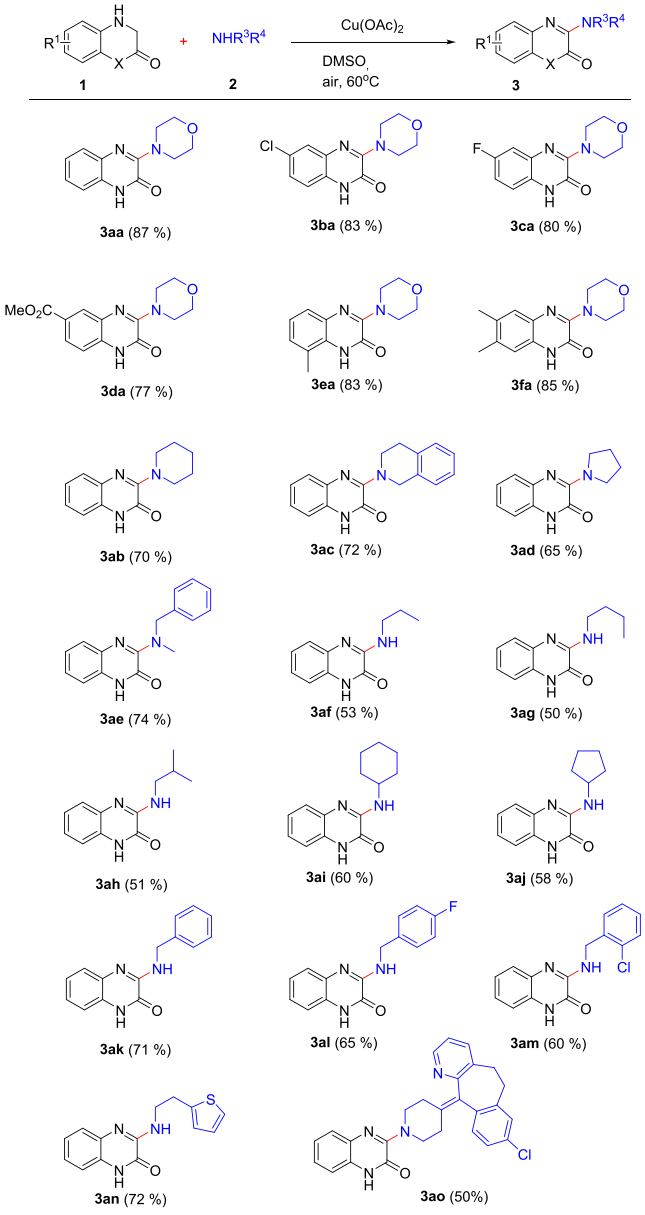


Entry	Catalyst	Oxidant	Solvent	Temp (°C)	Yield (%)
1	$Cu(OAc)_2$ (10 mol %)	air	DMSO	60	87
2	$CuCl_2$ (10 mol %)	air	DMSO	60	76
3	$Cu(acac)_2$ (10 mol %)	air	DMSO	60	33
4	$FeCl_3$ (10 mol %)	air	DMSO	60	-
5	$Cu(OAc)_2$ (10 mol %)	O_2	DMSO	60	84
6	$Cu(OAc)_2$ (10 mol %)	air	DCM	60	31
7	$Cu(OAc)_2$ (10 mol %)	air	MeCN	60	50
8	$Cu(OAc)_2$ (10 mol %)	air	EtOAc	60	26
9	$Cu(OAc)_2$ (10 mol %)	air	EtOH	60	51
10	$Cu(OAc)_2$ (10 mol %)	air	DMSO	70	77
11	$Cu(OAc)_2$ (10 mol %)	air	DMSO	50	69

Scheme 3. Screening of Reaction Conditions [a] Reaction Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), solvent (1 mL), 24 h. [b] Isolated yields.

O_2 atmosphere resulted in same efficiency (Scheme 3, entry 5). The use of other solvents such as CH_2Cl_2 (31%), MeCN (50%), EtOAc (26%) and EtOH (51%) was found to be less productive then DMSO (87%) (Scheme 3, entries 6–9). The variation of temperature suggested that 60 °C was the best choice for the transformation (Scheme 3, entries 10 and 11).

With the optimized reaction conditions in hand, the scope of the oxidative amination/aromatization tandem reaction was explored. Firstly, we applied the transformation to a range of 3,4-dihydroquinoxalin-2(1H)-ones **1** using morpholine (**2a**) as the reaction partner. Dihydroquinoxalinones (**1a–f**), including electron-donating or electron-withdrawing groups on the aromatic ring, worked well in this reaction (Scheme 4, 3aa-3fa). Subsequently, a variety of secondary aliphatic amines ranging from cyclic to acyclic derivatives were tested, and the corresponding products were isolated in moderate to high yields (Scheme 4, 3aa-3ae). After the successful demonstration of oxidative



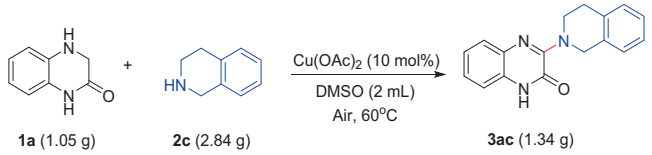
Scheme 4. Copper catalyzed aerobic amination aromatization tandem reaction of 3,4-dihydroquinoxalin-2(1H)-ones[a,b] [a] Reaction Conditions: **1** (0.2 mmol), **2** (0.6 mmol), DMSO (1 mL), 60 °C, air, 24 h. [b] Isolated yields.

amination of 3,4-dihydroquinoxalin-2(1H)-ones with secondary amines, the reaction was further explored with primary amines. A range of primary aliphatic and aromatic amines were found also suitable substrates to give high yields of the corresponding 3-aminoquinoxalinones (Scheme 4, 3af-3an). Moreover, an anti-allergic medicinal molecule desloratadine was suitable substrate in this transformation too (Scheme 4, 3ao). The scalability of the reaction was confirmed by carrying out a gram-scale synthesis starting from **1a** and **2c**. The desired product **3ac** was obtained in 68% yield (1.34 g) after 16 h of reaction time (Scheme 5).

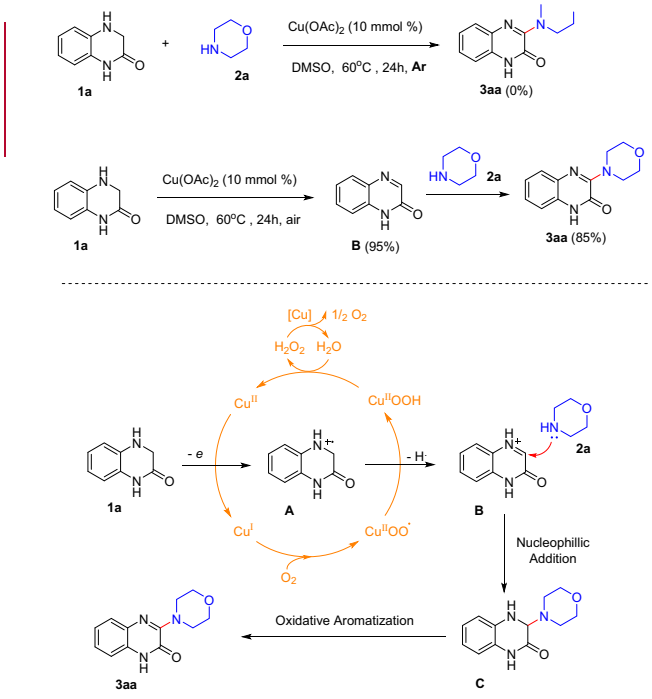
To understand the mechanism of this transformation, several control experiments were conducted. First of all, we observed that the template reaction of 3,4-dihydroquinoxalin-2(1H)-one **1a** with morpholine **2a** did not take place under argon atmosphere (Scheme 6, rxn. 1). On the other hand, the reaction of **1a** in the absence of **2a** under the standard reaction conditions was investigated. quinoxalin-2(1H)-ones **B** was isolated in an excellent yield (Scheme 6, rxn. 2). And the reaction of **B** with **2a** under standard reaction conditions was then investigated (Scheme 6, rxn. 2). The desired product **3aa** was obtained in a high yield. These results indicate that the quinoxalin-2(1H)-ones **B** is involved as a key intermediate and copper salt is the redox catalyst with air as terminal oxidant.

On the basis of the findings of control experiments, a possible mechanism is proposed in Scheme 6 (bottom half). The 3,4-dihydroquinoxalin-2(1H)-one **1a** was first one-electron oxidized to generate the radical cation intermediate **A** by copper (II) salt. The iminium ion intermediate **B** could then be formed through a hydrogen abstraction process from intermediate **A** by Cu(II)OO radical. Subsequently, nucleophilic addition of activated intermediate **B** with aliphatic amine **2a** occurred to give intermediate **C**. Finally, aromatization of intermediate **C** occurred under copper catalyzed aerobic conditions to generate the desired product **3aa**.

In summary, an efficient and practical copper catalyzed aerobic oxidative C(sp^3)–H amination and the following aromatization of 3,4-dihydroquinoxalin-2(1H)-ones was developed, which provides a possibility for the preparation of biologically active 3-aminoquinoxalinone derivatives from readily available starting materials. This amination reaction can be scaled up to gram level. Exploration of more type of oxidative dehydrogenative C—H functionalization reactions of 3,4-dihydroquinoxalin-2(1H)-ones and 3,4-dihydro-1,4-benzoxazin-2-ones are currently underway in our laboratory.



Scheme 5. Scale-up experiment and Late-stage transformation[a].



Scheme 6. Control experiments and proposed mechanism.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153271.

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