Organic LETTERS

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Copper-Catalyzed Aerobic Oxidative Amination of sp^3C-H Bonds: Efficient Synthesis of 2-Hetarylquinazolin-4(3*H*)-ones

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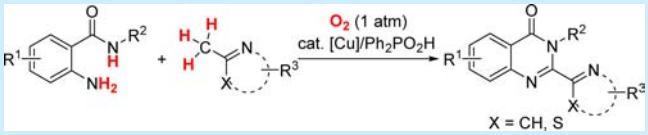
Supporting Information

ABSTRACT: An efficient synthesis of 2-hetarylquinazolin-4(3*H*)-ones via copper-catalyzed direct aerobic oxidative amination of sp^3C-H bonds has been developed. This tandem oxidation−amination−cyclization transformation represents a straightforward protocol to prepare 2-hetaryl-substituted quinazolinones from easily available 2-aminobenzamides and (2-azaaryl)methanes.



Quinazolin-4(3*H*)-one compounds, especially 2-heterocycle-substituted quinazolin-4(3*H*)-ones, constitute the key core units of many synthetic drugs and natural products.[1−3] For example, luotonin A[3a,b] has cytotoxicity toward human cancer lines, while bouchardatine[3c] occurs in the natural product *Bouchardatia neurococca* (Figure 1). Traditionally, quinazolin-4(3*H*)-ones are prepared by the oxidative condensation of *o*-aminobenzamide with aldehydes or carboxylic acid derivatives under acidic or basic conditions.[4−6] However, the corresponding aldehydes are usually expensive and chemically unstable for preparation and storage, while the acid derivatives only show low reactivity due to severe decarboxylation side reactions.[7] To overcome these drawbacks, alternative methods, such as intramolecular cyclization of *o*-haloanilides and oxidative condensation of *o*-aminobenzamide with alcohols, haloalkane, and amines, etc., have been developed.[8] Although these synthetic protocols serve well, these transformations require prefunctionalized substrates and usually suffer from poor atom economy. Thus, more straightforward methods for the preparation of quinazolin-4(3*H*)-one compounds from easily available substrates still remain highly desirable.

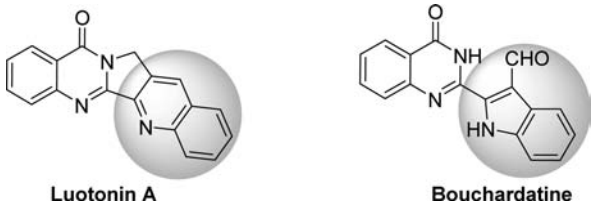
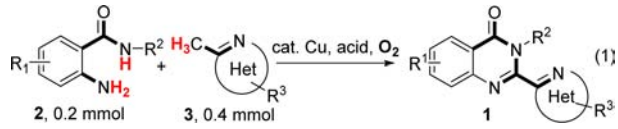


Figure 1. Examples of quinazolin-4(3*H*)-one fused natural product and synthetic drug.

Recently, the direct transformations of methylarenes and methylhetarenes have attracted increasing attention due to their recognized importance in biology, pharmacology, and organic synthesis.[9] However, examples of such reactions applied in the construction of *N*-heterocycles remain scarce.[10,11] Herein, we disclose an efficient synthesis of 2-hetarylquinazolin-4(3*H*)-ones **1** using the readily available 2-aminobenzamides **2** and (2-azaaryl)methanes **3** (eq 1). This transformation proceeds via Cu-catalyzed direct aerobic oxidative amination of sp^3C-H bonds.[12] Compared to conventional methods, this procedure is distinguished by using clean O_2 as an oxidant, avoiding the use of the dangerous hyperoxides and hypervalent iodine(III) reagents.[9d,11f,13] To the best of our knowledge, no similar examples have been reported for such a one-pot synthesis of 2-hetarylquinazolin-4(3*H*)-one directly from (2-azaaryl)methane **3**, which is cheap and readily available. This new method provides a totally convenient and environmentally friendly access to heterocyclic compounds **1** via a novel efficient oxidation−amination−cyclization tandem process.



As a model reaction, the reaction of 2-aminobenzamide **2a** with 2-methylpyridine **3a** under oxygen atmosphere (1 atm) was investigated first (Table 1), disclosing that a catalytic amount of copper and Ph_2PO_2H could promote the reaction efficiently. An extensive screening of the reaction conditions revealed that **1aa** was generated in 80% yield in the presence of a catalytic amount of CuCl and Ph_2PO_2H (run 5). All of the copper catalyst, acid and oxygen are essential for this reaction. The absence of any of them led to failure of the formation of the desired product **1aa** (runs 1−4). When less amount of catalyst CuCl/Ph_2PO_2H was

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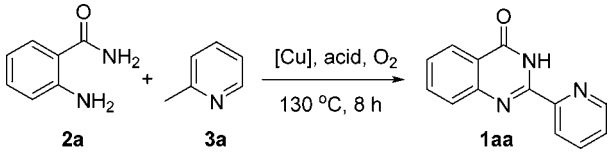
Table 1. Optimization of the Reaction Conditions[a]



2a 3a 1aa

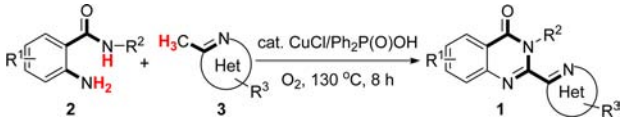
run	[Cu]	acid	solvent	yield[b] (%)
1			C_6H_5Cl	none
2	CuCl		C_6H_5Cl	none
3[c]		Ph_2PO_2H	C_6H_5Cl	none
4[d]	CuCl	Ph_2PO_2H	C_6H_5Cl	none
5	CuCl	Ph_2PO_2H	C_6H_5Cl	80
6[e]	CuCl	Ph_2PO_2H	C_6H_5Cl	55(76)
7[f]	CuCl	Ph_2PO_2H	C_6H_5Cl	35
8[g]	CuCl	Ph_2PO_2H	C_6H_5Cl	40
9	CuBr	Ph_2PO_2H	C_6H_5Cl	32
10	CuI	Ph_2PO_2H	C_6H_5Cl	22
11	$CuCl_2$	Ph_2PO_2H	C_6H_5Cl	68
12	$CuBr_2$	Ph_2PO_2H	C_6H_5Cl	31
13	$Cu(OAc)_2$	Ph_2PO_2H	C_6H_5Cl	27
14	CuCl	$PhCO_2H$	C_6H_5Cl	47
15	CuCl	$PhCH_2CO_2H$	C_6H_5Cl	60
16	CuCl	CF_3CO_2H	C_6H_5Cl	35
17	CuCl	Ph_2PO_2H	MeCN	27
18	CuCl	Ph_2PO_2H	THF	21
19	CuCl	Ph_2PO_2H	DCE	11
20	CuCl	Ph_2PO_2H	toluene	57
21	CuCl	Ph_2PO_2H	dioxane	65
22[h]	CuCl	Ph_2PO_2H	C_6H_5Cl	43

[a]Reaction conditions: **2a** (0.2 mmol), **3a** (0.4 mmol), copper catalyst (15 mol %), an acid (50 mol %), and solvent (1 mL) in a 25 mL sealed glass tube, O_2 (1 atm), 130 °C, 8 h. [b]GC yields using *n*-dodecane as an internal standard. [c]1 equiv of Ph_2PO_2H was used. [d]Conducted under nitrogen. [e]10 mol % of CuCl was used. Yield in parentheses refers to reaction performed for 24 h. [f]5 mol % of CuCl was used. [g]20 mol % of Ph_2PO_2H was used. [h]Under air.

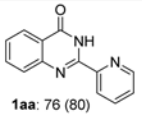
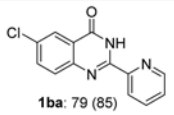
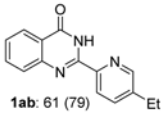
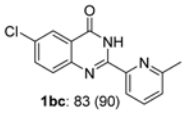
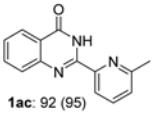
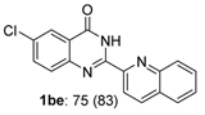
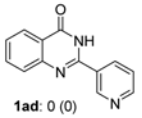
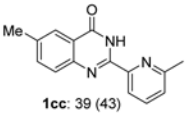
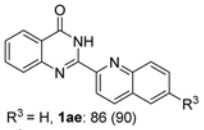
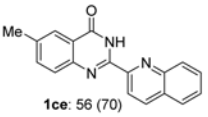
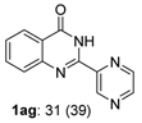
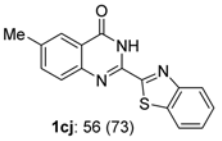
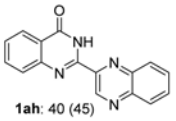
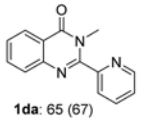
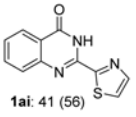
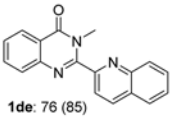
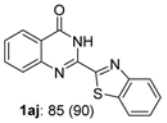
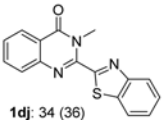
loaded, the yield of **1aa** decreased (runs 6−8). Among the copper catalysts investigated, CuCl showed the highest catalytic efficiency (Table 1, runs 9−13). As to the acid, although inferior to Ph_2PO_2H, carboxylic acids such as $PhCO_2H$, $PhCH_2CO_2H$, and CF_3CO_2H also catalyzed the reaction to give moderate yields of **1aa** (runs 14−16). As for the solvents (runs 17−21), the reaction also took place in toluene and dioxane to give good yields of the product but afforded low yields in acetonitrile, THF, and $ClCH_2CH_2Cl$ (DCE). Finally, the reaction could be carried out under air to give the product in a moderate yield (run 22).

As shown in Table 2, this aerobic oxidative amination can be applied to a variety of substrates to produce the corresponding 2-hetaryl-quinazolin-4(3*H*)-one **1** in good yields. In addition to this monosubstituted 2-methylpyridine **3a**, disubstituted 5-ethyl-2-methylpyridine **3b** and 2,6-dimethylpyridine **3c** also gave high yields of the corresponding products (runs 2 and 3). Noteworthy was that only the methyl group at the 2-position of **3b** was oxidatively aminated in this reaction. Very interestingly, a substrate with the methyl group at the 3-position (**3d**) did not react at all under the present reaction conditions (run 4). Similarly, 2-methylquinoline **3e** and 6-methoxy-2-methylquinoline **3f** also gave the expected condensation products **1ae** and **1af** in 86% and 56% yield, respectively (runs 5 and 6). In addition to these simple heterocycles, heterocycles fused multiple heteroatoms were also suitable substrates for this transformation. For

Table 2. Synthesis of 2-Hetarylquinazolin-4(3*H*)-ones 1[a]



2 3 1

run	yield[b] (%)	run	yield[b] (%)
1	 **1aa**: 76 (80)	11	 **1ba**: 79 (85)
2	 **1ab**: 61 (79)	12	 **1bc**: 83 (90)
3[c]	 **1ac**: 92 (95)	13	 **1be**: 75 (83)
4	 **1ad**: 0 (0)	14	 **1cc**: 39 (43)
5 6[d]	 R^3 = H, **1ae**: 86 (90) R^3 = MeO, **1af**: 56 (69)	15	 **1ce**: 56 (70)
7[e]	 **1ag**: 31 (39)	16	 **1cj**: 56 (73)
8	 **1ah**: 40 (45)	17	 **1da**: 65 (67)
9	 **1ai**: 41 (56)	18	 **1de**: 76 (85)
10	 **1aj**: 85 (90)	19	 **1dj**: 34 (36)

[a]Reaction conditions: **2** (0.2 mmol), **3** (0.4 mmol), CuCl (0.03 mmol, 15 mol %), Ph_2PO_2H (0.1 mmol), C_6H_5Cl (1 mL), 130 °C, 8 h. [b]Isolated yields (GC yields in parentheses) based on **2**. [c]20 mol % of CuCl, 4-nitrobenzoic acid (0.2 mmol), 150 °C, 18 h. [d]30 mol % of CuCl, 4-nitrobenzoic acid (0.2 mmol), 150 °C, 18 h. [e]63% of **3f** was recovered, whereas substrate **2a** was fully consumed.

example, both 2-methylpyrazine **3g** and 2-methylquinoxaline **3h** produced the corresponding condensation products **1ag** and **1ah** (runs 7 and 8). The reaction was further successfully applied to sulfur-containing 2-methylthiazole **3i** and 2-methylbenzothiazole **3j**, and the oxidative condensation products **1ai** and **1aj** were obtained in good yields under similar reaction conditions (runs 9 and 10). As for 2-aminobenzamides **2**, in addition to the simplest **2a**, the chloro-substituted **2b** and methyl-substituted **2c** also served as good substrates to produce the oxidative condensation products efficiently (runs 11−13 and 14−16). Importantly, the substituted *N*-methylbenzamide **2d** could also be employed in

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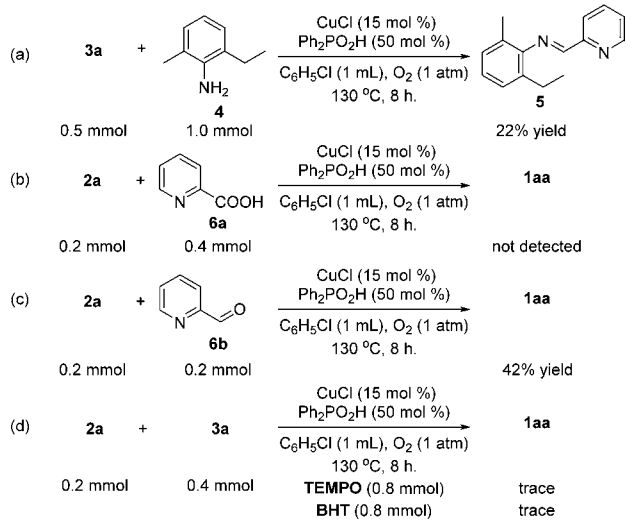
this reaction to give the corresponding condensation products in good yields (runs 17−19). It should be noted that these oxidative condensation products **1** are valuable synthetic intermediates for the synthesis of biologically active compounds.[1b] For example, luotonin A (Figure 1) can be easily prepared by using the product **1ae**.[14]

In order to obtain insight into the reaction mechanism, several control experiments were carried out (Scheme 1). First, by

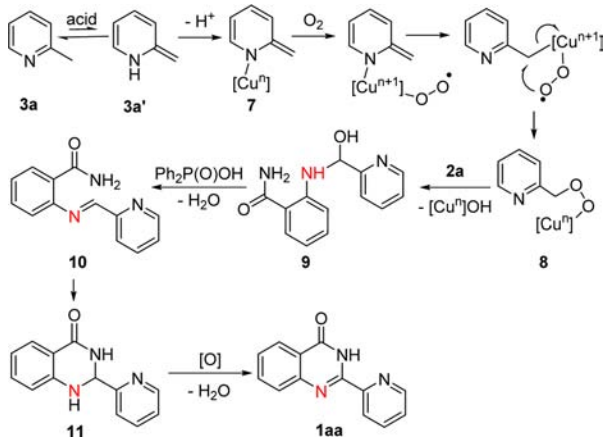
Scheme 1. Control Experiments



replacing **2a** with 2-ethyl-6-methylaniline **4** in the reaction with **3a**, an imine **5** was obtained in 22% yield,[15] indicating that an imine intermediate was involved in the above catalytic oxidative condensation process (Scheme 1, a). It was initially assumed that **3a** was oxidized to picolinic acid **6a**, which then reacted with **2a** to give **1aa**.[16] However, this possibility was readily ruled out because it was confirmed that a mixture of **2a** with picolinic acid **6a** under the standard conditions did not afford the product **1aa** (Scheme 1, b). When picolinaldehyde **6b** was allowed to react with **2a**, **1aa** was obtained in 42% yield (Scheme 1, c). This result indicated that aldehydes perhaps served as the efficient intermediate. Finally, the reaction was strongly retarded in the presence of a radical scavenger. For example, by addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT), only a trace of **1aa** was obtained, showing that radical intermediates were involved in this transformation (Scheme 1, d).

On the basis of the experiments described above and literature examples,[17] a possible mechanism for this aerobic oxidation cyclization reaction is outlined in Scheme 2. Since in the absence of an acid[18] or copper the reaction does not proceed, and the methyl group of **3** must be located at the 2-position (a similar reaction did not take place with 3-picoline **3i**), it is assumed that **3a** can be isomerized to a nonaromatic enamine intermediate **3a′**.[19,20] Moreover, it is confirmed that toluene does not react under the present conditions, indicating that the nitrogen atom of **3a** is crucial for the formation of a metal enamide intermediate **7**.[9j−m] Subsequent oxidation of **7** with O_2 generates intermediate **8**,[21a] which then reacts with **2a** to give **9**.[21b] Brønsted acid catalyzed dehydration of **9** affords the imine intermediate **10**, which is cyclized to give **11**. Finally, aerobic oxidation of **11** produces the product **1aa**.[22]

Scheme 2. Proposed Mechanism



In summary, we have disclosed an efficient copper-catalyzed aerobic oxidative sp^3C-H amination of (2-azaaryl)methanes leading to 2-hetarylquinazolin-4(3*H*)-ones using oxygen as the sole oxidant under mild conditions. Three sp^3C-H and three N−H bonds are removed in this novel chemistry to produce the highly valuable *N*-heterocycles from readily available materials. Further extension and synthetic applications of this Cu-catalyzed oxidative C−H amination method are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization, mechanistic studies, and ^1H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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