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Synthesis of Pyrido-Fused Quinazolinone Derivatives via Copper-Catalyzed Domino Reaction

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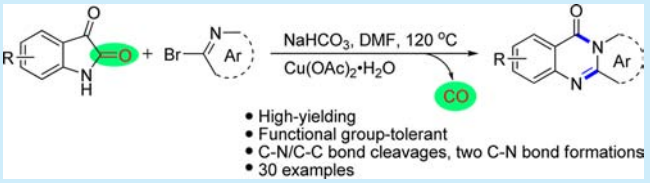
Supporting Information

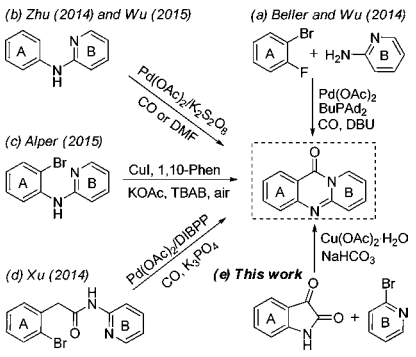
ABSTRACT: A simple and efficient synthesis of 11*H*-pyrido[2,1-*b*]quinazolin-11-ones by $Cu(OAc)_2 \cdot H_2O$-catalyzed reaction of easily available substituted isatins and 2-bromopyridine derivatives has been developed. The reaction involves C−N/C−C bond cleavage and two C−N bond formations in a one-pot operation. This methodology is complementary to previously reported synthetic procedures, and two plausible reaction mechanisms are discussed.



As an important class of nitrogen-containing heterocycles, quinazolinone is one of the ubiquitous structural motifs that occur in natural products and pharmaceutically active molecules.[1−3] Numerous attractive methods have been reported for the preparation of functionalized quinazolinones.[4,5]

Fused quinzolinones, especially pyrido-fused quizolinones, are of pariticular pharmaceutical value. For example, 7,8-dehydrorutaecarpine, 1-hydroxy-7,8-dehydrorutaecarpine, euxylophoricine B, euxylophoricine E, and euxylophoricine F are important biologically active natural alkaloids bearing a 11*H*-pyrido[2,1-*b*]quinazolin-11-one fragment isolated from the plants (see Supporting Information).[6,7] The general method for the synthesis of tricyclic pyrido-fused quinazolinones[8] involves the lactamization of 2-(pyridin-2-ylamino)benzoic acid, which is prepared by the reaction of 2-chlorobenzoic acid and 2-aminopyridine.[9] Recently, Beller and Wu reported a base-controlled selective synthesis of liner and angular pyrido-fused quinazolinones by palladium-catalyzed carbonylation/nucleophilic aromatic substitution sequence (Scheme 1, path a).[10] Zhu illustrated an efficient synthesis of 11*H*-pyrido[2,1-*b*]quinazolin-11-ones via a palladium-catalyzed C−H carbonylation of *N*-aryl-2-aminopyridines by using carbon monoxide as the carbonyl source in the presence of oxidant $K_2S_2O_8$ (Scheme 1, path b).[11] DMF could also be used as carbon monoxide surrogate in this reaction.[12] Alper demonstrated that 11*H*-pyrido[2,1-*b*]-quinazolin-11-ones could be prepared by palladium-catalyzed dearomatizing carbonylation from *N*-(2-bromophenyl)pyridine-2-amines (Scheme 1, path c).[13] Xu found that the tricyclic or tetracyclic fused quinazolinones could be synthesized by a copper-catalyzed domino reaction from arylacetamides involving an aerobic benzylic oxidation/cyclization/decarbonylation process (Scheme 1, path d).[14] Despite the significant progress made in this field, the existing methods often require the use of expensive metal catalysts or starting materials that are not readily available. Moreover, most of these methods have difficulty in accessing valuable halo-substituted products due to undesired metal-catalyzed dehalogenation reactions. Accordingly, novel synthetic approaches to the pyrido-fused quinazolinones, with enhanced reaction efficiency as well as improved availability of starting materials, are still highly desirable. In a continuation of our efforts to develop new synthetic protocols for building valuable heterocyclic frameworks,[15] herein we report an efficient copper-catalyzed domino synthesis of 11*H*-pyrido[2,1-*b*]-quinazolin-11-one derivatives from 2-bromopyridines and readily accessible isatins,[16] a type of starting material that has been widely employed in organic, medicinal, and material synthesis (Scheme 1, path e).[17−19]

Scheme 1. Pathways for the Synthesis of Pyrido-Fused Quinazolinones



At the start of our study, the model reaction of isatin (**1a**) and 2-bromopyridine (**2a**) was conducted in the presence of CuO (2.0 equiv) in DMF at 150 °C in an effort to synthesize *N*-pyridinyl-substituted isatin 1-(pyridin-2-yl)indoline-2,3-dione.[20] However, no desired product was observed, and the yellow solid precipitated, which was isolated to give the unexpected 11*H*-

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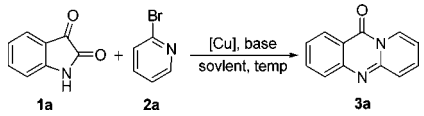
pyrido[2,1-*b*]quinazolin-11-one (**3a**) in 76% yield (Table 1, entry 1). Then, we attempted to reduce the loading of copper salt

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

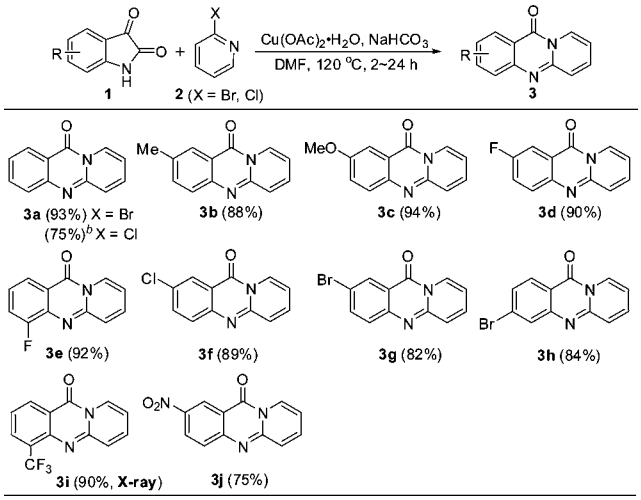
entry	catalyst (equiv)	base (equiv)	solvent	temp (°C)	yield[b] (%)
1	CuO (2.0)	none	DMF	150	76[c]
2	CuO (0.2)	$NaHCO_3$	DMF	120	35
3	Cu_2O (0.2)	$NaHCO_3$	DMF	120	87
4	CuI (0.2)	$NaHCO_3$	DMF	120	89
5	CuBr (0.2)	$NaHCO_3$	DMF	120	84
6	CuCl (0.2)	$NaHCO_3$	DMF	120	90
7	$Cu(OAc)_2$ (0.2)	$NaHCO_3$	DMF	120	82
8	**$Cu(OAc)_2·H_2O$ (0.2)**	**$NaHCO_3$**	**DMF**	**120**	**93**
9	$Cu(OAc)_2·H_2O$ (0.2)	Na_2CO_3	DMF	120	91
10	$Cu(OAc)_2·H_2O$ (0.2)	K_2CO_3	DMF	120	90
11	$Cu(OAc)_2·H_2O$ (0.2)	NEt_3	DMF	120	62
12	$Cu(OAc)_2·H_2O$ (0.3)	$NaHCO_3$	DMF	120	93
13	$Cu(OAc)_2·H_2O$ (0.1)	$NaHCO_3$	DMF	120	85
14	$Cu(OAc)_2·H_2O$ (0.2)	$NaHCO_3$	DMF	90	52
15	$Cu(OAc)_2·H_2O$ (0.2)	$NaHCO_3$	DMSO	120	88
16	$Cu(OAc)_2·H_2O$ (0.2)	$NaHCO_3$	*n*-PrOH	reflux	70
17	$Cu(OAc)_2·H_2O$ (0.2)	$NaHCO_3$	toluene	reflux	trace
18	$Cu(OAc)_2·H_2O$ (0.2)	$NaHCO_3$	dioxane	reflux	trace
19	$Cu(OAc)_2·H_2O$ (0.2)	$NaHCO_3$	*t*-BuOH	reflux	0
20	none	$NaHCO_3$	DMF	120	0
21	$Cu(OAc)_2·H_2O$ (0.2)	none	DMF	120	38

[a]Unless otherwise specified, all of the reactions were carried out using isatin (**1a**, 1.0 mmol), 2-bromopyridine (**2a**, 1.2 mmol), and base (2.0 mmol) in solvent (5 mL) for 10 h in the presence of catalyst. [b]Isolated yield. [c]The reaction was carried out for 2 h.

and lower the reaction temperature, and it was found that in the presence of $NaHCO_3$ (2.0 equiv) and 0.2 equiv of CuO at 120 °C, the reaction could furnish **3a** in 35% yield (entry 2). After screening other typically used copper salts, such as Cu_2O, CuI, CuBr, CuCl, $Cu(OAc)_2$, and $Cu(OAc)_2·H_2O$ (0.2 equiv), the reaction gave **3a** in best yield (93%) when $Cu(OAc)_2·H_2O$ was used as the catalyst (entries 3−8). Inorganic bases such as Na_2CO_3 and K_2CO_3 were also effective for this reaction, affording **3a** in 91% and 90% yield, respectively (entries 9, 10), while the organic base Et_3N gave the product in moderate yield (entry 11). Increasing the loading of catalyst led to less significant improvement, but the reaction gave a slightly lower yield when reducing the amount of catalyst to 0.1 equiv (entries 12 and 13). Decreasing the reaction temperature to 90 °C resulted in a lower yield (entry 14). Other polar solvents such as DMSO and *n*-PrOH also delivered the product in 88% and 70% yield, respectively (entries 15 and 16). Nearly no reaction occurred in nonpolar and lower boiling point solvents (entries 17−19). **3a** was not formed in the absence of $Cu(OAc)_2·H_2O$ (entry 20), and the reaction gave **3a** in 38% yield even without additional base probably due to the weak basic nature of 2-bromopyridine and the product (entry 21).

With the aforementioned optimized reaction conditions in hand (Table 1, entry 8), reactions between a variety of substituted isatins (**1**) and 2-halopyridines (**2**) were investigated, and good substrate scope was observed (Scheme 2). Specifically,

Scheme 2. Scope of Isatins[a]



[a]Unless otherwise specified, all of the reactions were carried out using substituted isatins (**1**, 1.0 mmol), 2-bromopyridine (**2a**, 1.2 mmol), $Cu(OAc)_2·H_2O$ (0.2 mmol), and $NaHCO_3$ (2.0 mmol) in DMF (5 mL). Isolated yield. [b]Using 2-chloropyridine (**2b**, 1.2 mmol) at 150 °C for 14 h.

the reaction of relatively less active 2-chloropyridine with isatin at 150 °C gave **3a** in 75% yield. Isatins bearing electron-donating (-Me and -OMe) or electron-withdrawing groups (-F, -Cl, -Br, $-CF_3$, and $-NO_2$) on the phenyl ring was reacted smoothly with 2-bromopyridine to deliver the corresponding 11*H*-pyrido[2,1-*b*]quinazolin-11-one derivatives **3b−j** in good to excellent yields (75−94%). The structure of **3i** was confirmed by X-ray single-crystal diffraction analysis (Figure 1).

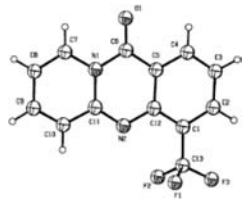


Figure 1. X-ray structure of compound **3i**.

Encouraged by the results achieved above, the substrate scope was further examined, as shown in Scheme 3. It was found that 3-, 4-, and 5-position methyl substituted 2-bromopyridines were tolerated in this transformation to furnish the corresponding **4a−c** in good yields. The slightly lower yield of **4d** was possibly attributed to the steric hindrance of the 2-bromo-6-methylpyridine. Substrates with methoxy, halogen (-F, -Cl, and -Br), and CF_3 substituents on the pyridine ring were smoothly converted into the corresponding **4e−i** in 75−91% yields. These results are

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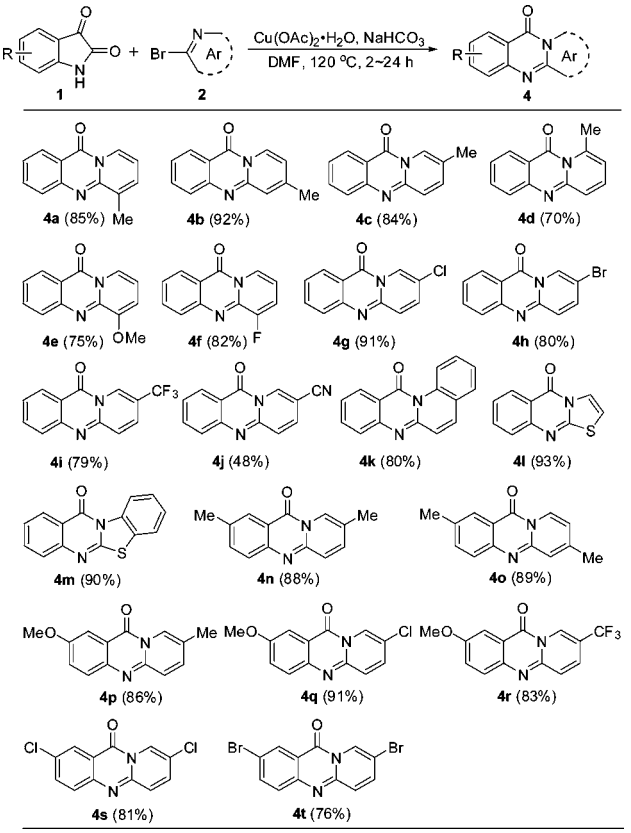
Scheme 3. Scope of 2-Bromopyridine Derivatives[a]



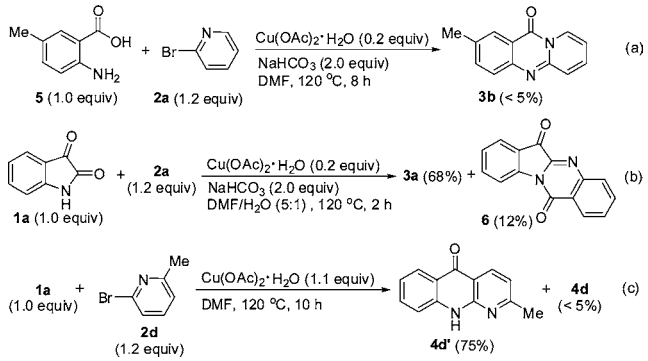
[a]Unless otherwise specified, all of the reactions were carried out using substituted isatins (**1**, 1.0 mmol), 2-bromopyridine derivatives (**2**, 1.2 mmol), $Cu(OAc)_2·H_2O$ (0.2 mmol), and $NaHCO_3$ (2.0 mmol) in DMF (5 mL). Isolated yield.

particularly worth noting as halo-substituted 11*H*-pyrido[2,1-*b*]quinazolin-11-ones, which could be transformed to other functionalized molecules by C−C or C−N cross-coupling reactions, have been problematic substrates for the previous reported methods due to the undesired dehalogenation reactions.[10,13,14] The presence of nitriles appeared to partially inhibit the reaction, evidenced by the modest yield (48%) obtained for **4j**. 2-Bromoquinoline, 2-bromothiazole, and 2-bromobenzo[*d*]thiazole were also suitable substrates for the reaction, affording the products **4k**−**m** in 80−93% yields. Demonstrating the structural diversity of target molecules, some representative disubstituted 11*H*-pyrido[2,1-*b*]quinazolin-11-ones **4n**−**t** were also obtained in good results under the standard reaction conditions.

Importantly, an attempted direct reaction of 2-amino-5-methylbenzoic acid (**5**) with 2-bromopyridine under the above standard conditions only led to the product **3b** in <5% yield, highlighting the importance of isatin in this novel reaction (Scheme 4a). When the mixture of DMF/H_2O (5:1, v/v) was used as the solvent, **3a** was obtained in 68% yield within 2 h. Meanwhile, the natural alkaloid indolo[2,1-*b*]quinazoline-6,12-dione (**6**, tryptanthrin) was isolated in 12% yield, which was likely to undergo the self-condensation of isatin and its hydrolysis product 2-(2-aminophenyl)-2-oxoacetic acid (Scheme 4b; see Supporting Information).[21] Apparently, the C−N bond cleavage occurred in the presence of water and sodium bicarbonate.

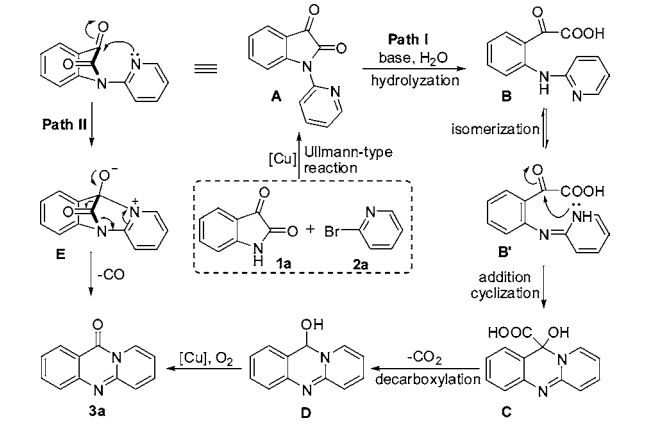
On the basis of these results and previously reported work, a preliminary reaction mechanism was proposed using the

Scheme 4. Controlled Experiments



synthesis of **3a** as an example (Scheme 5). Initially, a copper-catalyzed Ullmann-type coupling reaction[22] of isatin and 2-

Scheme 5. Possible Reaction Mechanism



bromopyridine gave the *N*-substituted intermediate 1-(pyridin-2-yl)indoline-2,3-dione **A**. The byproduct hydrogen bromide (HBr) would be neutralized with sodium bicarbonate to release water and carbon dioxide. **A** then could undergo two possible pathways to give the final product **3a**. For pathway I, in the presence of base, the hydrolysis of **A** would deliver a keto-acid intermediate **B**,[21,23] which can be isomerized to form imine **B′**.[24] The ensuing intramolecular addition cyclization reaction would generate a six-membered ring intermediate **C** via the Pfitzinger-type reaction.[21b,25] The subsequent decarboxylation/aerobic oxidation reaction promoted by copper and air would furnish the conjugated target molecule **3a**.[26] For pathway II, the direct intramolecular nucleophilic attack of pyridine nitrogen atom to ketone would afford a tricyclic zwitterionic intermediate **E**, which could be converted to **3a** after the extrusion of carbon monoxide, and a similar mechanism has been proposed by Xu's group.[14] It was also found that in the absence of base $NaHCO_3$, when 1.1 equiv of $Cu(OAc)_2·H_2O$ was used, 2-methylbenzo[*b*][1,8]-naphthyridin-5(10*H*)-one (**4d′**) was isolated as the major product in 75% yield, and **4d** was only obtained in <5% yield (Scheme 4c), which indicated the possible extrusion of the carbon monoxide process (see Supporting Information).

In summary, we have described a simple and efficient method for the synthesis of pyrido-fused quinazolinone derivatives catalyzed by $Cu(OAc)_2·H_2O$ from substituted isatins and 2-bromopyridine derivatives. The C−N/C−C bond cleavage and two C−N bond formations were observed in a one-pot operation. Two plausible reaction mechanisms are also

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proposed. The prominent advantages of this route are the (1) easily available starting materials; (2) wide scope of substrates with further functionalization potentials; and (3) low cost catalyst $Cu(OAc)_2 \cdot H_2O$ with good to excellent yields of desired products. This methodology is complementary to previous synthetic procedures. Further investigations on the applications of this transformation for other functionalized heterocyclic systems and on the clarification of the mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00113.

General experimental procedure and characterization data of the products (PDF)
X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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