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Report

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Copper-Catalyzed Aerobic Oxidative Ring Expansion of Isatins: A Facile Entry to Isoquinolino-Fused Quinazolinones

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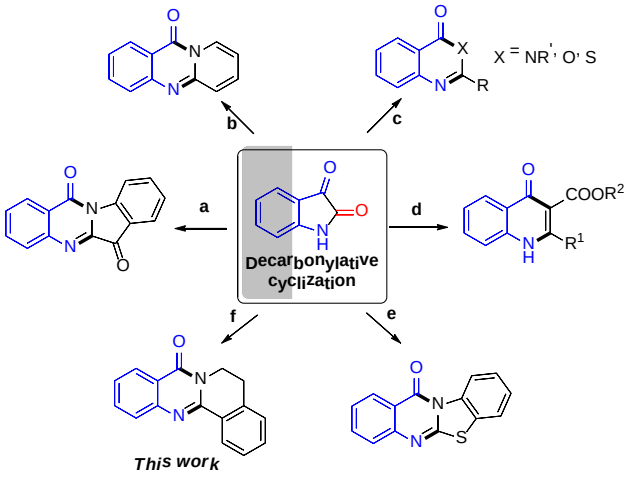
Summary of main observation and conclusion A copper-catalyzed aerobic oxidative ring expansion reaction of isatins with 1,2,3,4-tetrahydroisoquinoline for the synthesis of tetracyclic quinazolinones has been developed. This reaction is performed smoothly under simple conditions to give the corresponding products in moderate to good yields with good functional group tolerance. The capacity of the resultant 5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one for a range of palladium-catalyzed directing C-H activation has been further demonstrated, thus giving a broader access to diverse tetracyclic quinazolinones.

Background and Originality Content

Quinazolinone and its derivatives are privileged structural frameworks among valuable molecules possessing diverse biological and medicinal activities,[1-2] such as Luotonin A-anticancer,[2a] Mackinazolinone-antidepressant,[2b] and Rutaecarpine-antithrombotic activity.[2c] Generally, classic methods for the synthesis of this compound motif depend on cyclic condensation of *o*-aminophenylformamide with aldehydes or their substitutes.[3] Nevertheless, most reactions suffer from certain limitations, such as the need for inaccessible starting materials, harsh reaction conditions, and excessive oxidant.[4] In this regard, the development of concise methods for the construction of diverse quinazolinones from easily accessible starting materials under simple conditions is highly desirable.



Scheme 1. Decarbonylative cyclization of isatin.

Isatin (1*H*-indole-2,3-diones) is a subclass of the indole family that has been employed in the discovery of biological scaffolds or anticancer medicines.[5] Hence, isatin and their derivatives have been attracting considerable interest in molecular synthesis. In recent years, the synthesis of nitrogen-containing heterocycles has been actively explored through isatin ring-expansion. Common methods for the ring-expansion reaction of isatins and their derivatives are as follows: 1) ring-expansion through the cleavage of the C2-N1 bond with enamines to synthesize multisubstituted quinoline-4-carboxamides derivatives;[6] 2) ring-formation through the insertion of atoms into the C2-C3 bond or C3-C4.[7] For example, Zou and co-workers reported an efficient and practical method for the construction of benzimidazo[l,2-*c*]quinazolin-6- ones through the cleavage of the C2–C3 bond to and insertion of heteroatoms using molecular

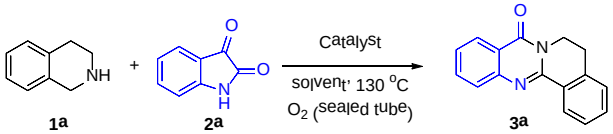
oxygen as the oxidant.[7a] And Interestingly, Bathini described an efficient regioselective ring expansion reaction of isatins with aldehydes for the synthesis of *α*-aryl/heteroaryldiazomethane through the insertion of aldehydic carbonyl into the C3-C4 bond.[7c]

Over the past decade, the development of the synthesis of nitrogen-containing heterocycles through the decarbonylative cyclization of isatins has been extensively studied. [8-11] For instance, in 2013, Wang's group developed a concise method for the synthesis of tryptanthrins from commercially available indoles and isatins (Scheme 1, a).[8] In 2016, Huang's group found an appealing strategy for the synthesis of pyrido-fused quinazolinone derivatives by Cu-catalyzed decarbonylative cyclization of substituted isatins and 2-bromopyridine derivatives (Scheme 1, b).[9] Sanjib and co-workers described the copper(II)-catalyzed decarboxylative coupling reactions of isatins arylglyoxylic acids with arylglyoxylic acids involving C-N and C-O bond formation, isatins affording 4H-benzo[*d*][1,3]oxazin-4-ones involving C-N and C-O bond formation.[10a] In 2020, Wu and Chen disclosed an $FeCl_3$-mediated cascade coupling/decarbonylative annulation reaction of isatin with fluorinated imidoyl chlorides (Scheme 1, c).[10b] Likewise, Wu's group also reported a series of Baeyer-Villiger-type pathway for the synthesis of nitrogen-containing heterocycles (Scheme 1, c-e).[11] Very recently, Jia and co-workers developed a TFA/TBHP-promoted oxidative cyclisation of isatins with 1,2,3,4-tetrahydroisoquinolines.[11e] Within our own on-going program on sustainable oxidation reactions to construct heterocycles,[12] herein, we present a copper-catalyzed isatin decarbonylative cyclization with 1,2,3,4-tetrahydroisoquinoline (THIQ) to synthesize tetracycline tetracyclic quinazolinones with 1,2,3,4-tetrahydroisoquinoline (THIQ) enabling two C–N bond formation (scheme 1, f).

Results and Discussion

Initially, THIQ (**1a**) and isatin (**2a**) were selected as model substrates to evaluate the feasibility and selectivity of this transformation. To our pleasure, the mixture of **1a** and **2a** simply stirred at 130 °C under oxygen atmosphere (sealed tube) led to the formation of the isoquinolino-fused quinazolinone product **3a** (18% yield). Then, transition metal catalyst screening revealed the corresponding product **3a** was obtained in 62% yield when the reaction was carried out with $CuSO_4$ in DMSO at 130 °C for 24 h, while other metal salts such as $FeCl_3$, $Mn(OAc)_2$, $PdCl_2$, Ag_2O, and $NiCl_2$ did not significantly promote the reaction (entries 2−7). Encouraged by these results, we further screened other copper catalysts such as CuCl, $CuCl_2$, $Cu(OAc)_2$, CuI, and $Cu(OTf)_2$ (entries 8-12). To our delight, the formation of **3a** was observed in 83% yield when the catalyst was replaced by $Cu(OTf)_2$ (entry 12). The investigation of solvent effect revealed that PhCl demonstrated the best performance, while DMF, PhCl, $PhCH_3$, and 1,4-dioxane were proved to be unsuitable reaction media (entries 13-16). Decreasing the temperature of this reaction afforded an inferior result (entry 17). Finally, no desired product was detected when the reaction was performed under argon atmosphere (entry 18).

Table 1 Optimization of the reaction condition[a]



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

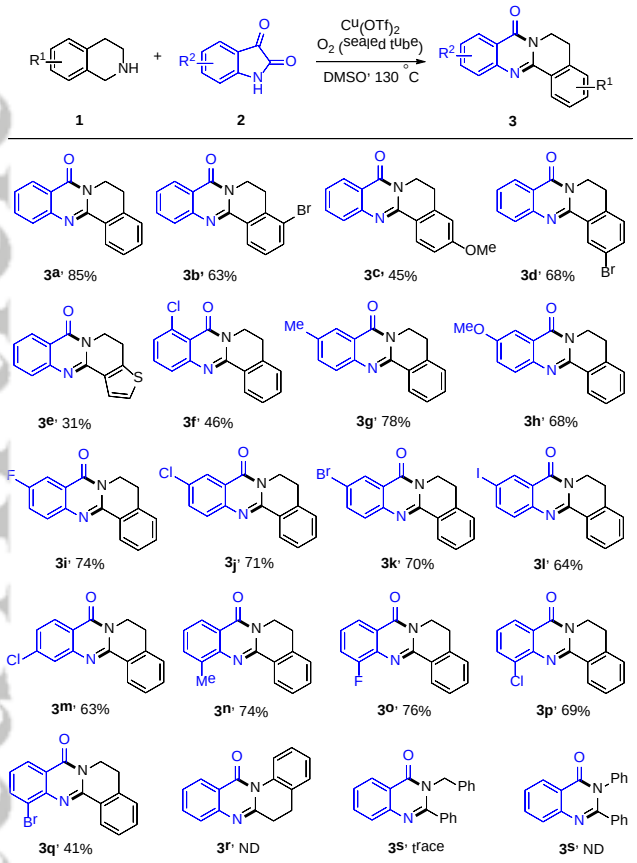
Entry	Catalyst	Solvent	Yieldb (%)
1	none	DMSO	18
2	$FeCl_3$	DMSO	26
3	$Mn(OAc)_2$	DMSO	24
4	$PdCl_2$	DMSO	18
5	Ag_2O	DMSO	19
6	$NiCl_2$	DMSO	trace
7	$CuSO_4$	DMSO	62
8	CuCl	DMSO	55
9	$CuCl_2$	DMSO	39
10	$Cu(OAc)_2$	DMSO	41
11	CuI	DMSO	56
12	$Cu(OTf)_2$	DMSO	83
13	$Cu(OTf)_2$	DMF	47
14	$Cu(OTf)_2$	PhCl	trace
15	$Cu(OTf)_2$	$PhCH_3$	trace
16	$Cu(OTf)_2$	1,4-dioxane	trace
17[c]	$Cu(OTf)_2$	DMSO	74
18[d]	$Cu(OTf)_2$	DMSO	0

[a] Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (15 mol%), solvent (0.6 mL), 130 °C, 24 h, under O_2. [b] GC yields. [c] 120 °C. [d] under Ar.

With the optimized reaction conditions in hand, we next investigated the substrate scope for the synthesis of tetracyclic quinazolinones. The results are summarized in Table 2. The model reaction of THIQ (**1a**) and isatin (**2a**) gave the desired product **3a** in 85% isolated yield. Then, THIQs bearing various substituents could smoothly couple with isatin (**2a**). When 5-bromo-1,2,3,4-tetrahydroisoquinoline (**1b**) and 7-bromo-1,2,3,4-tetrahydroisoquinoline (**1d**) were employed, the corresponding product **3b** and **3d** were obtained in 63% and 68% yields, respectively. Slightly lower yield was obtained when the methoxy group was located at the C-6 position in the isoquinoline ring (**3c**). It is worth noting that the 4,5,6,7-tetrahydrothieno- [3,2-*c*]pyridine was also suitable in this reaction and afforded the corresponding products **3e** in 31% yield. The substituent position significantly affected the reaction yield and the reaction yield decreased dramatically when functional group chloro (**2f**) was located at the C-4 position in isatin. Better yields were obtained when the functional groups such as methyl (**2g** and **2n**), methoxy (**2h**), fluoro (**2i** and **2o**), chloro (**2j**, **2m** and **2p**), bromo (**2k** and **2q**) and iodine (**2l**) were located at C-5, C-6 and C-7 position. It appeared that various electron-donating and electron-withdrawing substituents were well tolerated in the reaction and there was no straightforward correlation between

the electronic properties of the substituents and reaction efficiency. It should be noted that the cleavage of C–halogen bonds (even C-I bond) was not observed in our copper catalysis, as determined by GC-MS analysis.

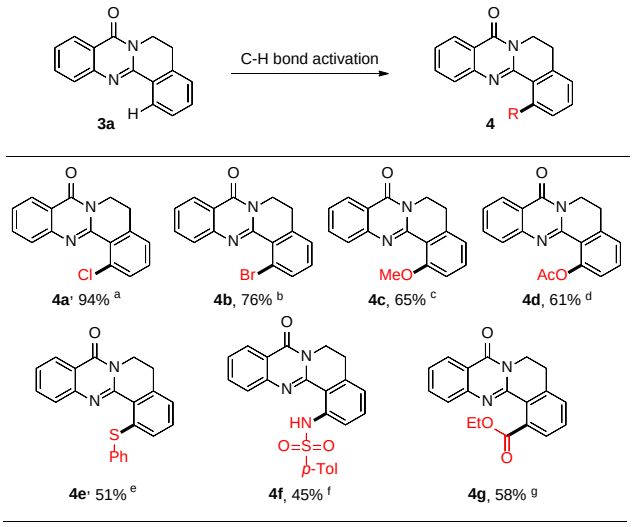
Table 2 Substrate scope.[a]



[a] *Conditions*: **1** (0.2 mmol), **2** (0.3 mmol), Cu(OTf)$_2$ (15 mol%), DMSO (0.6 mL), 130 °C, 24 h, under O_2. Isolated yield based on **1**.

Directing C-H bond functionalization has emerged as a powerful tool in organic synthesis.[13] Functional group-assisted C-H bond cleavage shows great promise to the control of site selectivity.[14] We attempted to conduct further transformation to other structurally novel molecules through C-H activation of tetracyclic quinazolinones.[15] A series of C-H activation reactions have proved feasible when using **3a**. This is the first reported using quinazolinones as directing group for C-H bond functionalization. The halogenation products **4a** and **4b** could be obtained in 94% and 76% yields, respectively, when using *N*-chlorosuccinimide or *N*-bromosuccinimide as halogen source and oxidant. The reaction of **3a** with Pd(II)/PhI(OAc)$_2$ system in methanol solvent produced methoxylation product **4c** in 65% yield. Pd-catalyzed acetoxylation of **3a** furnished the expected product **4d** in 61% yield. The sulfenylation of **3a** was demonstrated by Pd-catalyzed C–S bond formation *via* C–H cleavage using diphenyl disulfide, which gave the corresponding product **4e** in 51% yield. Moreover, Rh-catalyzed directing amidation of **3a** using sulfonyl azides as the amine source afforded the desired product **4f** in moderate yield. Finally, the Pd-catalyzed reaction of **3a** with diethyl azodicarboxylate DEAD and $K_2S_2O_8$ furnished the product esters **4g** in 58% yield.

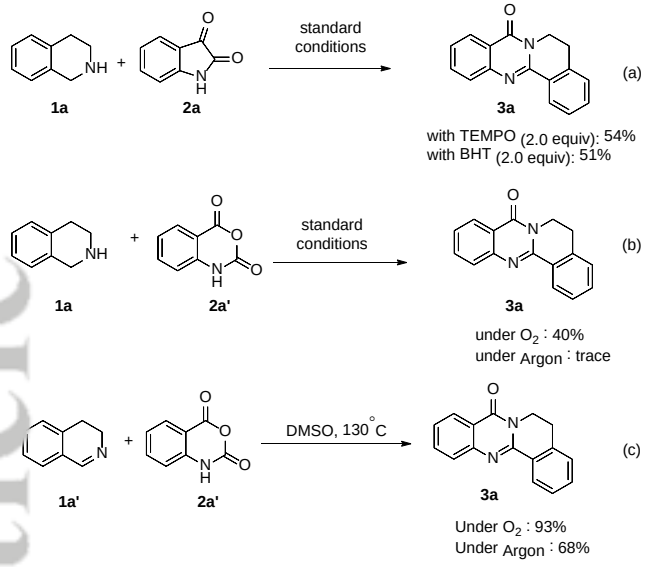
Scheme 2. Further direct C–H bond functionalization of **3a.**



Reaction conditions: (a) **3a** (0.2 mmol), Pd(OAc)$_2$ (5 mol%), NCS (1.2 equiv.), CH_3CN (1 mL), 100 °C, 72 h. (b) **3a** (0.2 mmol), Pd(OAc)$_2$ (5 mol%), NBS (1.2 equiv.), CH_3CN (1 mL), 100 °C, 36 h. (c) **3a** (0.2 mmol), Pd(OAc)$_2$ (5 mol%), PhI(OAc)$_2$ (2.0 equiv.), CH_3OH (1 mL), 100 °C, 24 h. (d) **3a** (0.2 mmol), Pd(OAc)$_2$ (5 mol%), PhI(OAc)$_2$ (2.0 equiv.), CH_3CN (1 mL), 100 °C, 72 h. (e) **3a** (0.2 mmol), diphenyl disulfide (0.3 mmol), Pd(OAc)$_2$ (10 mol%), CuBr (2.0 equiv.), DMF (1 mL), 140 °C, N_2, 72 h. (f) **3a** (0.2 mmol), *p*-toluenesulfonyl azide (0.22 mmol), $[RhCp^*Cl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%.), 1,2-DCE (0.5 mL), 80 °C, N_2, 12 h. (g) **3a** (0.2 mmol), Pd(OAc)2 (5 mol%), DEAD (2.0 equiv.), $K_2S_2O_8$ (0.6 equiv.), DCE (0.5 mL), 100 °C, 6 h.

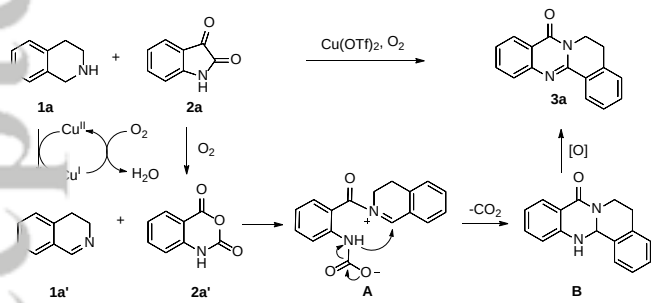
To gain insight into reaction mechanism, several control experiments were conducted. First, The addition of radical scavengers TEMPO (2,2,6,6-tetramethylpiperidinooxy) and BHT (2,6-di-*tert*-butyl-4-hydroxytoluene) to the reaction system did not obviously influence this reaction, which indicates that a radical pathway might not be involved in this reaction (Scheme 3, a). The product **3a** was obtained in 40% yield when isatoic anhydride **2a'**, which may be generated by Baeyer-Villiger-type oxidation of isatins, was used as the substrate with **1a** under O_2 atmosphere, and trace yield was obtained under Ar atmosphere (Scheme 3, b). This result indicates that isatin is probably oxidized by O_2 in the initial step to form the intermediate **2a'**. The treatment of the hypothesized intermediate **1a'** with intermediate **2a'** in the absence of copper catalyst could be harvested to the target product **3a** in 93% yield under oxygen atmosphere, while 68% yield under argon atmosphere (Scheme 3, c).

Scheme 3 Control experiments under various conditions.



According to the above control experiments and related references, a proposed mechanism for **3a** formation is illustrated in Scheme 4.[16] Accordingly, 1,2,3,4-tetrahydroisoquinoline **1a** is oxidized to 3,4-dihydroisoquinoline **1a'** in the presence of Cu/O_2. Isatoic anhydride **2a'** is formed through the oxidation of **2a** under a oxygen atmosphere. Then the condensation reaction between **1a'** and **2a'** generate the intermediate **A**. Subsequently, an intramolecular attack of the nitrogen atom to imine carbocation followed by releasing a molecule of carbon dioxide provides the tetracyclic intermediate **B**. Finally, the desired products **3a** is obtained through dehydrogenative oxidation of **B**.

Scheme 4 Proposed mechanism.



Conclusions

In conclusion, we have demonstrated a Cu-catalyzed decarbonylative ring-opening reaction of isatin with 1,2,3,4-tetrahydroisoquinoline for the synthesis of tetracycline quinazolinones in moderate to good yields. Environmentally friendly molecular oxygen is used as the oxidant. This method exhibits good functional group tolerance and easy operation. Meanwhile, more diversity tetracycline quinazolinone derivatives can be obtained by group-assisted C-H bond functionalization. Further studies on functionalization of indole family are ongoing in our laboratory.

Experimental

General procedure: (3a)

A 10 mL reaction vessel was charged with 1 (0.2 mmol), 2 (0.3 mmol), $Cu(OTf)_2$ (0.015 mmol), DMSO (0.6 mL) under O_2. The reaction vessel was stirred at 130 °C for 24 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (5 mL) and washed with saturated sodium chloride solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate for three times. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to yield the desired product **3a** as yellow solid (42.2 mg, 85%).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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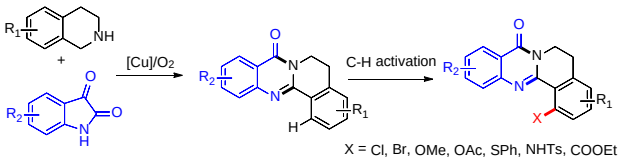

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