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Concise construction of 12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-ones *via* an unusual TBHP/Na_2CO_3 promoted cascade oxidative cyclization and interrupted Dimroth rearrangement

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An efficient transition-metal-free cascade reaction has been developed for the facile synthesis of 12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-one derivatives from commercially available isatins and 2-haloaryl isothiocyanates. A preliminary mechanistic study suggested an interrupted Dimroth rearrangement was the key step for the successful transformation.

Benzothiazolo[2,3-*b*]quinazolinone scaffolds are important structural motifs in various biologically active agents and functional molecules (Fig 1). They exhibit an extensive range of promising biological activities, including cytotoxicity against HL-60, inhibitory activities towards EGFR, anti-bacterial, antiviral and antitumor activities.[1] Moreover, owing to its distinct electrochemical properties, 8,9-dihydroxy-7-methyl-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one can be applied to electrochemical sensors for glutathione, amoxicillin or *L*-cysteine.[2]

Due to their great importance, a series of methods has been developed for the construction of benzothiazolo[2,3-*b*]quinazolinones. Traditionally, molecules with such a scaffold were synthesized from 2-aminobenzoic acids and 2-halobenzoic acids (or their derivatives) *via* a nucleophilic aromatic substitution and acylation sequence.[3] Several other methods have been established for the preparation of benzothiazolo[2,3-*b*]quinazolinones, but some have limitations such as multiple synthetic steps, harsh reaction conditions, or limited substrate scope.[4] Recently, Huang and Yin reported an elegant copper-catalyzed domino reaction towards the benzothiazolo[2,3-*b*]quinazolinone scaffold triggered by an Ullmann coupling (eqn (1), Scheme 1).[5] Xu also demonstrated that benzothiazolo[2,3-*b*]quinazolinones can be obtained by an effective copper-catalyzed oxidation/amination/decarbonylation sequence of pre-synthesized arylactetamides (eqn (2), Scheme 1).[6] Despite these fulfilling methods discovered in recent years, the development of concise methods towards benzothiazolo[2,3-*b*]quinazolinones, especially under metal-free conditions, is still highly desirable in terms of step economy, reaction efficiency, and substrate availability.

Isatins, a unique structure possessing a γ-lactam and a ketone, have been employed extensively since the early 19th century for the construction of a wide range of biologically useful compounds.[7] On account of its potential to serve as both an electrophile and a nucleophile, various reactions have been established using isatins or its derivatives as a substrate.[8] Recently, the development of isatin-based reactions mainly

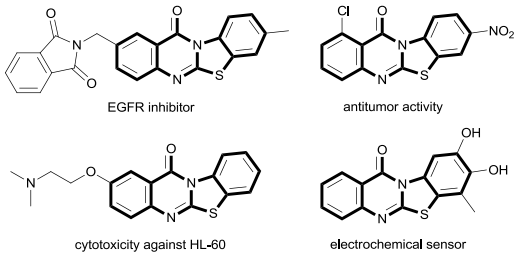

Fig 1. Representative functional benzothiazolo[2,3-b]quinazolinone scaffolds.

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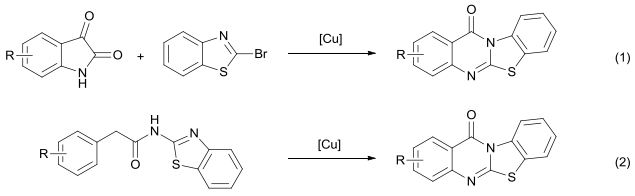
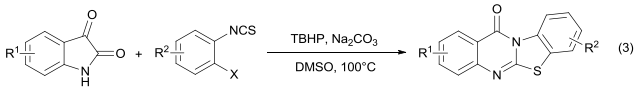
Electronic Supplementary Information (ESI) available: Experimental details, characterization of compounds, copies of ^1H and ^{13}C spectra for selected compounds, and CIF files of **3f**. See DOI: 10.1039/x0xx00000x

Previous work: Transition-metal-catalyzed cascade reactions



This work: Transition-metal-free cascade reactions



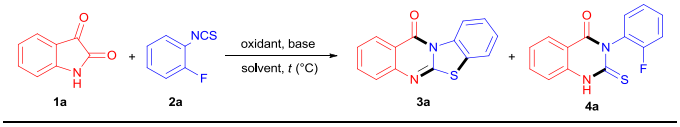
Scheme 1 Recent advances for the preparation of benzothiazolo[2,3-*b*]quinazolinones

focused on nucleophilic additions to the C-3 carbonyl group,[9] spiro-annulations,[10] ring-expansions,[5,6,10a,11] decarboxylative couplings[12] and C-H activations[13]. However, ring-expansions, especially transition-metal-free ring-expansions[11a] of isatins, are still relatively rare. Recently, we disclosed an elaborate ring-expansion reaction of isatins for the divergent synthesis of quinazolin-4(3*H*)-ones and tryptanthrins, enabled by a synergetic *tert*-butyl hydroperoxide (TBHP)/K_3PO_4 promoted oxidative cyclization.[11a] In conjunction with our ongoing research into developing isatin-based oxidative cyclization methodologies for valuable heterocycles,[11a,12] herein we present a transition-metal-free cascade oxidative cyclization for the convenient access to various 12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-one derivatives in one pot (eqn (3), Scheme 1). This method uses commercially available starting materials, occurs under mild conditions, and is compatible with a wide substrate scope. Notably, an interrupted Dimroth rearrangement[14] served as the key step for this smooth transformation. To the best of our knowledge, this is the first example of using an interrupted Dimroth rearrangement to synthesize N-heterocycles.

Initially, isatin (**1a**) and 1-fluoro-2-isothiocyanatobenzene (**2a**) were selected as the model substrates to examine the feasibility of this oxidative cyclization in the presence of TBHP and K_3PO_4 in DMSO at 100 °C in a sealed vessel under air. Gratifyingly, the reaction proceeded smoothly, and the desired 12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-one (**3a**) was obtained in 45% yield (Table 1, entry 1). Encouraged by this preliminary result, we continued to evaluate the effect of various inorganic and organic bases, with Na_2CO_3 giving the highest yield (Table 1, entries 2–8). Further screening of oxidants revealed that the green oxidant H_2O_2 could also promote this reaction smoothly, albeit in lower yield (Table 1, entry 9). Other oxidants such as DTBP or DDQ failed to deliver the target product (Table 1, entries 10, 11). Further survey of reaction media suggested that DMSO was the best choice of solvent (Table 1, entries 12–14). A diminished yield was obtained when the reaction was performed at a lower or higher temperature (Table 1, entries 15, 16), while the employment of an aqueous solution of TBHP demonstrated that the reaction was also compatible with a small amount of water (Table 1, entry 17). Finally, the optimal conditions were determined as **1a** (0.5 mmol), 1 equiv of **2a**, 1.5 equiv of TBHP and 3 equiv of Na_2CO_3 in DMSO at 100 °C for 9h.

Having established optimal reactions conditions, we then sought to evaluate the generality of this oxidative cyclization process. As shown in Table 2, we were pleased to find that the reaction demonstrated wide scope for isatins. Electron-donating groups (5-Me, 5-OMe and 6-OMe) proved to be favorable for this transformation, affording the desired products in excellent yields (**3b**–**3d**, 78–88%). In addition, an array of halogen-substituted isatins, including fluoro-, chloro- and bromo- at the C-4, C-5 or C-6 position, underwent the desired reaction smoothly, delivering the corresponding products in moderate to good yields (**3e**–**3k**, 55–77%), which provided opportunities for further synthetic elaboration. The 7-fluoro substituted isatin was also tolerated in this reaction, albeit in a lower yield of 33% (**3l**). It is worth noting that 1-fluoro, 1-chloro, 1-bromo and 1-iodo-2-isothiocyanatobenzenes were all compatible with these reaction conditions without any transition-metal catalysts.[15]

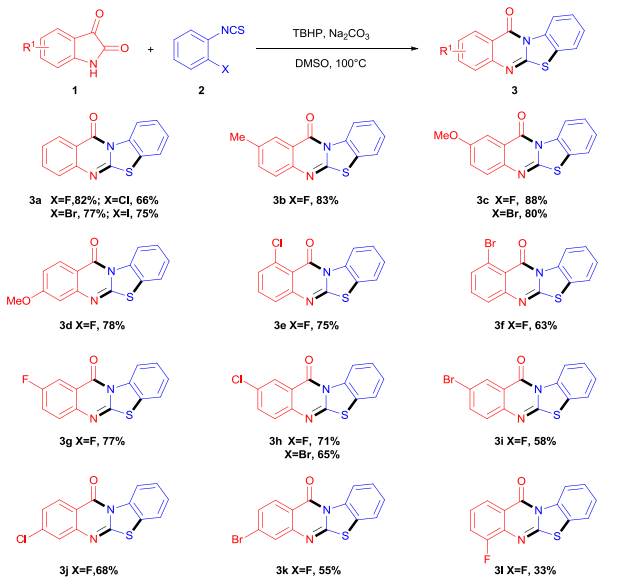
Table 1 Optimization studies



Entry	Base	Oxidant[c]	Solvent	*t* (°C)	Yield[b] (%)
1	K_3PO_4	TBHP	DMSO	100	45(33)
2	K_2CO_3	TBHP	DMSO	100	68(12)
3	Na_2CO_3	TBHP	DMSO	100	82(<5)
4	Cs_2CO_3	TBHP	DMSO	100	61(15)
5	Li_2CO_3	TBHP	DMSO	100	73(10)
6	NaOH	TBHP	DMSO	100	72(19)
7	DBU	TBHP	DMSO	100	56(7)
8	DABCO	TBHP	DMSO	100	trace(trace)
9	Na_2CO_3	H_2O_2	DMSO	100	55(9)
10	Na_2CO_3	DTBP	DMSO	100	trace(trace)
11	Na_2CO_3	DDQ	DMSO	100	trace(trace)
12	Na_2CO_3	TBHP	DMF	100	55(38)
13	Na_2CO_3	TBHP	NMP	100	31(43)
14	Na_2CO_3	TBHP	CH_3CN	reflux	trace(trace)
15	Na_2CO_3	TBHP	DMSO	90	72(<5)
16	Na_2CO_3	TBHP	DMSO	110	74(<5)
17[d]	Na_2CO_3	TBHP	DMSO	100	78(<5)

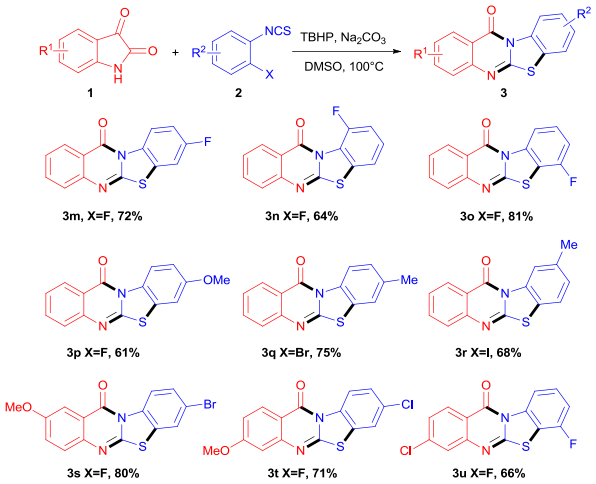
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), base (1.5 mmol), oxidant (0.75 mmol) were heated in 4 mL solvent in a sealed vessel under air for 9 h. [b]Isolated yield. Yield of side product **4a** was given in parenthesis. [c]TBHP (5.5 M in decane); H_2O_2 (30% aqueous solution); DTBP = di-*tert*-butyl peroxide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. [d]TBHP (70% aqueous solution).

Table 2 Substrate scope of isatins[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), Na_2CO_3 (1.5 mmol), TBHP (0.75 mmol) were heated in DMSO (4mL) at 100°C in a sealed vessel under air for 9 h. [b]Isolated yield.

Table 3 Substrate scope of 2-haloaryl isothiocyanates[a,b]



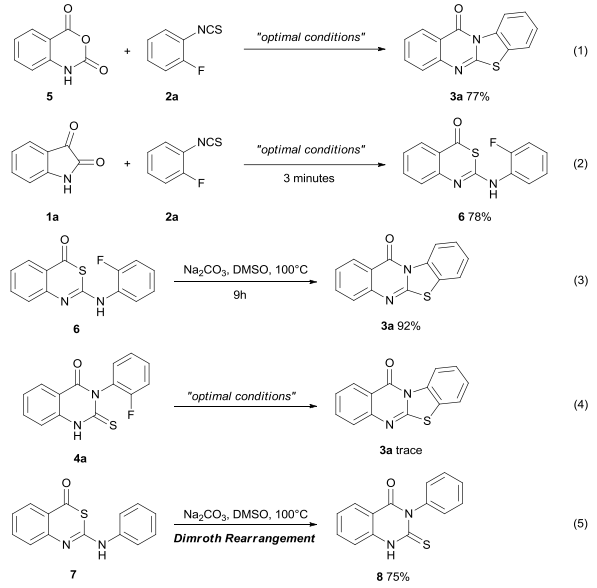
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), Na_2CO_3 (1.5 mmol), TBHP (0.75 mmol) were heated in DMSO (4mL) at 100°C in a sealed vessel under air for 9 h. [b]Isolated yield.

The fluoro-, bromo- and iodo-substituted substrates demonstrated greater reactivity over the chloro-substituted substrates, furnishing the corresponding molecules in higher yields (**3a**, **3c** and **3h**).

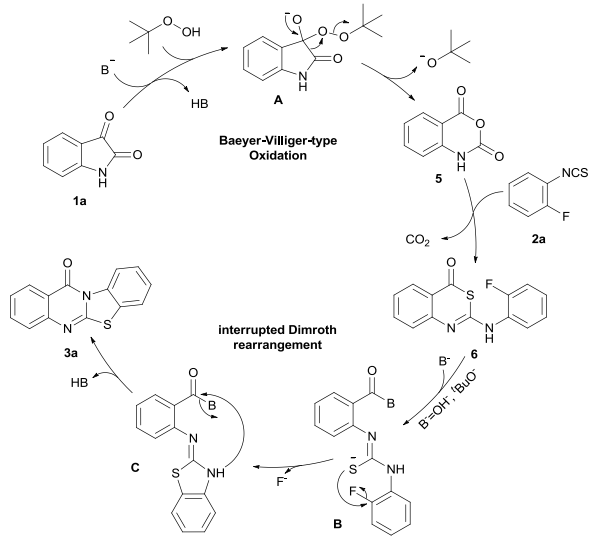
Inspired by this result, we continued to evaluate the diversity of substituted 2-haloaryl isothiocyanates. As highlighted in Table 3, the electronic properties and substitution positions on the phenyl ring exert little influence on the outcome of the reaction. Substrates bearing halogenic substituents such as 3-F, 4-F and 6-F were well tolerated, delivering the target structures in good to high yields (**3m–3o**, 64%–81%). Substitution at C-6 on the phenyl ring led to a small decrease in the yield, which was probably due to steric hindrance. Electron-donating groups (4-OMe, 4-Me, 5-Me) had a slight adverse effect on the reaction outcome (**3p–3r**, 61%–75%). To our delight, the reaction also proceeded smoothly with other halogenated substrates to give the corresponding products in good to high yields (**3s–3u**, 66–80%).

To shed light on the mechanism of this oxidative cyclization reaction, a series of control experiments were conducted as shown in Scheme 2. Initially, when isatoic anhydride (**5**) and 1-fluoro-2-isothiocyanatobenzene (**2a**) were mixed under optimal conditions, the desired product 12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-one (**3a**) was obtained in 77% yield (eqn (1), Scheme 2). Additionally, when isatin (**1a**) and 1-fluoro-2-isothiocyanatobenzene (**2a**) were subjected to the reaction under the optimal conditions for 3 min, 2-((2-fluorophenyl)amino)-4*H*-benzo[*d*][1,3]thiazin-4-one (**6**) was isolated in 78% yield (eqn (2), Scheme 2). Further treatment of **6** in the presence of Na_2CO_3 in DMSO at 100 °C gave the desired product **3a** in 92% yield (eqn (3), Scheme 2). These experiments indicated that isatoic anhydride (**5**) and benzothiazinone (**6**) might be intermediates in this reaction. To probe the pathway of the transformation from **6** to **3a**, 3-(2-fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**4a**) was synthesized and treated under optimal conditions; surprisingly, only a trace amount of the target product was formed (eqn (4), Scheme 2). To further illustrate whether the reaction proceeded through the Dimroth rearrangement, 2-(phenylamino)-4*H*-benzo[*d*][1,3]thiazin-4-one (**7**) was prepared and subjected to optimal conditions, and the corresponding product from the Dimroth rearrangement, 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**8**), was formed in 75% yield (eqn (5), Scheme 2). These results clearly demonstrated that the Dimroth rearrangement of **6** was interrupted by intramolecular nucleophilic aromatic substitution.

On the basis of the above results and literature precedents, a possible mechanism was proposed using isatin (**1a**) and 1-fluoro-2 isothiocyanatobenzene (**2a**) as an example (Scheme 3). Initially, isatin (**1a**) transformed into intermediate **A** by TBHP/Na_2CO_3 mediated nucleophilic attack, followed by an intramolecular rearrangement to generate isatoic anhydride



Scheme 2 Control experiments



Scheme 3 Possible mechanism

(**5**), the product of a Baeyer-Villiger-type oxidation[16]. The decarboxylative cyclization between isatoic anhydride (**5**) and 1-fluoro-2-isothiocyanatobenzene (**2a**) would give the benzothiazinone intermediate **6**. Subsequently, the Dimroth-rearrangement of **6** was interrupted by intramolecular aromatic nucleophilic substitution, giving intermediate **C**. Finally, the intramolecular amidation of **C** would deliver the target molecule **3a**.

In summary, a transition-metal-free cascade oxidative cyclization reaction for the facile synthesis of 12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-one derivatives has been developed. Preliminary mechanistic study suggested that the reaction proceeds through consecutive oxidation, decarboxylative cyclization, and interrupted Dimroth rearrangement. Further applications of this isatin-based oxidative cyclization strategy for the synthesis of other interesting heterocycles are currently underway in our laboratory.

Acknowledgements

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