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Divergent Synthesis of Quinazolin-4(3*H*)-ones and Tryptanthrins Enabled by a *tert*-Butyl Hydroperoxide/K_3PO_4-Promoted Oxidative Cyclization of Isatins at Room Temperature

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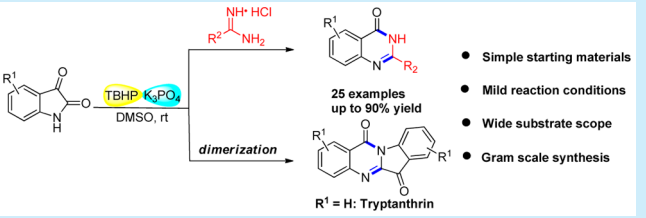
Supporting Information

ABSTRACT: A synergetic *tert*-butyl hydroperoxide/K_3PO_4-promoted oxidative cyclization has been developed for the facile synthesis of various functionalized quinazolin-4(3*H*)-ones from commercially available isatins and amidine hydrochlorides at room temperature. The synthetic utility of this strategy was illustrated by the convenient synthesis of tryptanthrin derivatives via a self-dimerization of isatins under the same conditions.



The quinazolinone nucleus is exemplified as a privileged structure that widely exists in natural products,[1,2] such as 2-methyl-4(3*H*)-quinazolinone,[1a] luotonins **A**, **B**, **E**, and **F**,[1b,c] tryptanthrin,[1c] and rutaecarpine[1d] (Figure 1). Quinazolinone

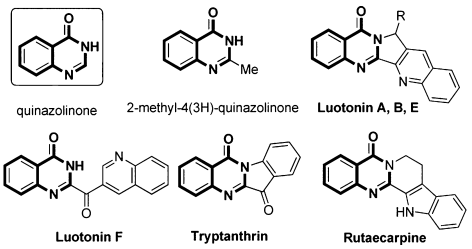
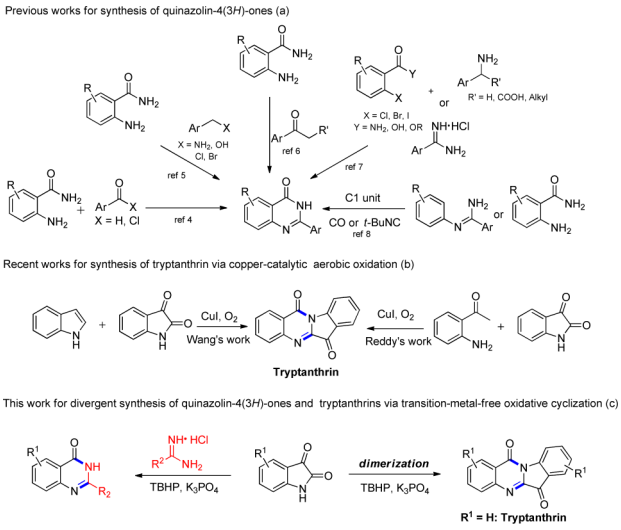


Figure 1. Quinazolinone skeleton containing natural products.

derivatives are also known to possess a range of biological and medicinal activities including antibacterial, antiviral, anti-inflammatory, and anticancer properties.[2] Futhermore, quinazolinone derivatives are also used as inhibitors of various enzymes.[3]

Because of their great value, the synthesis of quinazolinones has attracted extensive attention. Representative synthetic methods of this skeleton are mainly summarized as the following five types: (i) condensation of 2-aminobenzamides with aldehydes or acyl chlorides;[4] (ii) oxidation/cyclization reaction of 2-aminobenzamides with benzylamines, benzyl alcohols, or benzyl halides;[5] (iii) condensation/C−C bond cleavage of 2-aminobenzamides with carbonyl compounds;[6] (iv) coupling/cyclization reaction of *o*-halogen benzoic acid derivatives with amidines or benzylamines;[7] (v) domino reaction using palladium-catalyzed carbon monoxide or isocyanide insertion as the key step[8] (Scheme 1a). Although these reactions provide efficient accesses to quinazolin-4(3*H*)-

Scheme 1. Synthetic Routes to Quinazolin-4(3*H*)-one and Tryptanthrin Derivatives



ones, their applications are limited by poor substitution diversity or the requirement for harsh reaction conditions. Therefore, the development of concise methods for the facile construction of diverse quinazolin-4(3*H*)-ones is highly desirable.

Tryptanthrin, as a kind of natural quinazoline alkaloid, was isolated from the indigo plant *Strobilanthes cusia* (Acanthaceae).[9] Various approaches[10−12] were explored for efficient construction of this significant skeleton because of its

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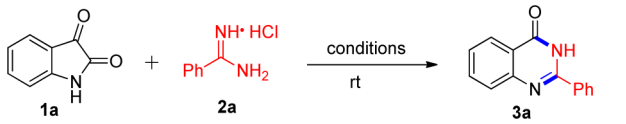
widespread biological and pharmaceutical activities.[13] Among these, the oxidative cyclization of isatins or its analogues have received considerable attention in light of the availability of starting materials. Traditionally, such processes require highly toxic oxidants such as $KMnO_4$ or $POCl_3$ and have low efficiencies.[10] Recently, Wang and co-workers proposed a graceful synthesis of tryptanthrins from indoles via the copper-catalyzed aerobic oxidation (Scheme 1b).[11] In addition, Reddy and co-workers[12] developed a copper-catalyzed domino oxidative cyclization strategy for the construction of tryptanthrins from 2-aminoaryl methyl ketones and isatins. Herein, we present an ambient-temperature *tert*-butyl hydroperoxide (TBHP)/K_3PO_4-promoted domino oxidative cyclization for the divergent synthesis of quinazolin-4(3*H*)-ones and tryptanthrins (Scheme 1c). Advantages of this method include the use of commercially available starting materials, mild reaction conditions, and good functional group compatibility.

In our previous work, we have disclosed an efficient domino protocol for the synthesis of 2-(1,3,4-oxadiazol-2-yl)aniline derivatives by employing copper-catalyzed intramolecular decarboxylative coupling as the key step.[14] Then our attention switched to develop new domino reaction involving copper-catalyzed intermolecular decarboxylative coupling. Our study commenced with the reaction of isatin (**1a**) and benzamidine hydrochloride (**2a**) in the presence of CuI, TBHP, and K_2CO_3 in DMSO at room temperature (25−30 °C) in a sealed vessel under air. Gratifyingly, the desired 2-phenylquinazolin-4(3*H*)-one (**3a**) identified by NMR spectra was obtained in 82% yield. To our surprise, a slight yield increase was observed in the absence of CuI. After investigating various reaction parameters including bases, oxidants, and solvents, the optimized reaction conditions were eventually identified as **1a** (0.5 mmol), 1.2 equiv of **2a**, 1.5 equiv of TBHP, and 3 equiv of K_3PO_4 in 4 mL of DMSO at room temperature for 6 h (Table 1 and see the Supporting Information).

The substrate scope was subsequently examined, as shown in Scheme 2. Various isatins (**1a**−**m**) with different electronic properties effectively underwent the oxidative annulation reactions with **2a** to provide the corresponding products in moderate to good yields (42−89%, **3a**−**m**). Substitutions at 4-, 5-, 6-, and 7- positions were all tolerated. The greater reactivity of the substrates containing an electron-withdrawing group at the 5-position of the aryl ring could lead to formation of the corresponding quinazolin-4(3*H*)-ones in higher yields (compared **3b**,**c** to **3d**,**e**). Steric hindrance had an obvious effect on this transformation (compared **3j**−**m** to **3a**−**i**). Notably, the quinazoline scaffolds were formed with a diverse range of halogen atoms, providing enormous possibilities for further modification. The reaction was attempted with a range of amidine hydrochlorides under the optimized conditions. It was found that the reaction conditions were compatible with both electron-rich (4-Me and 3-MeO) and halogenic (4-Cl) substituents on the phenyl rings of the benzamidine hydrochloride, which yielded the corresponding products in satisfactory yields (65−90%, **3n**−**p**). The aliphatic and heteroaryl amidine reagents (acetamidine hydrochloride, cyclopropane-1-carboximidamide hydrochloride, and isonicotinimidamide hydrochloride) were also found to be suitable for this transformation (84−87%, **3q**−**s**).

Having established the scope of our new domino reaction, the reaction mechanism was then evaluated. We initially investigated the reaction of isatin (**1a**) under the optimized conditions in the absence of benzamidine hydrochloride (**2a**),

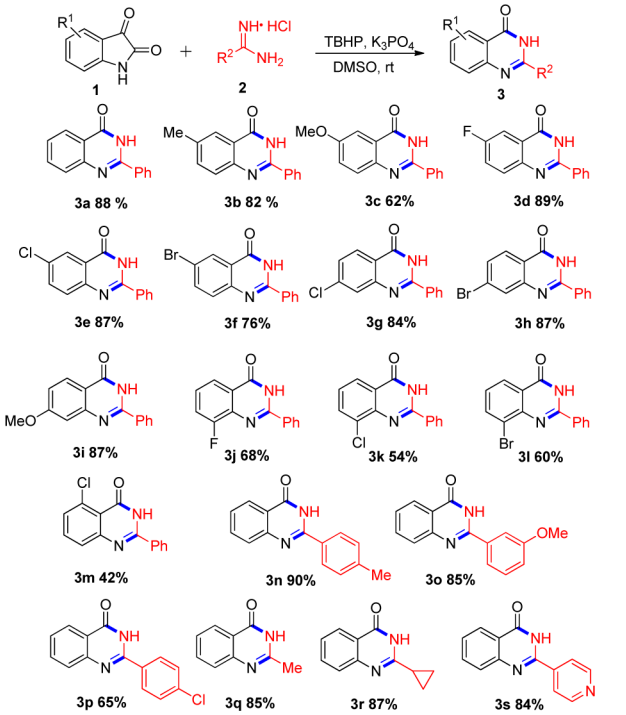
Table 1. Optimization of the Reaction Conditions[a]



entry	base	oxidant	solvent	yield[b] (%)
1	K_2CO_3	TBHP	DMSO	85
2	Na_2CO_3	TBHP	DMSO	83
3	Cs_2CO_3	TBHP	DMSO	82
4	**K_3PO_4**	**TBHP**	**DMSO**	**88**
5	KOH	TBHP	DMSO	78
6	K_3PO_4	*m*-CPBA	DMSO	trace
7	K_3PO_4	DDQ	DMSO	trace
8	K_3PO_4	PIDA	DMSO	8
9	K_3PO_4	$K_2S_2O_8$	DMSO	trace
10	K_3PO_4	DTBP	DMSO	trace
11	K_3PO_4	DBP	DMSO	trace
12	K_3PO_4	TBPB	DMSO	trace
13	K_3PO_4	TEMPO	DMSO	trace
14[c]	K_3PO_4	TBHP	DMSO	86
15	K_3PO_4	TBHP	DMF	87
16	K_3PO_4	TBHP	EtOH	61
17	K_3PO_4	TBHP	CH_3CN	75
18	K_3PO_4	TBHP	H_2O	trace

[a]Reactions conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), base (1.5 mmol), and oxidant (0.75 mmol) were added at room temperature (25−30 °C) in 4 mL of solvent in a sealed vessel under air for 6 h. [b]Isolated yield. [c]TBHP (5.5 M in decane).

Scheme 2. Scope of Isatins and Amidine Hydrochlorides[a,b]



[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), K_3PO_4 (1.5 mmol), and TBHP (0.75 mmol) in DMSO (4 mL) at room remperature (25−30 °C) in a sealed vessel under air for 6 h. [b]Isolated yields.

which unexpectedly afford natural product tryptanthrin (**4a**) in 90% yield (Scheme 3a). Interestingly, when isatin (**1a**, 2 equiv)

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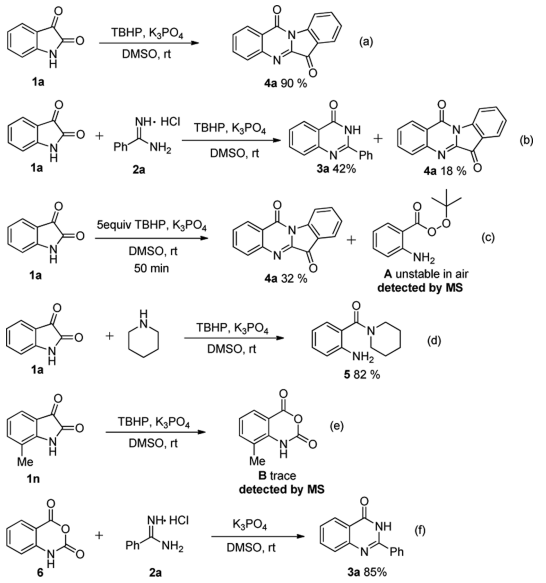
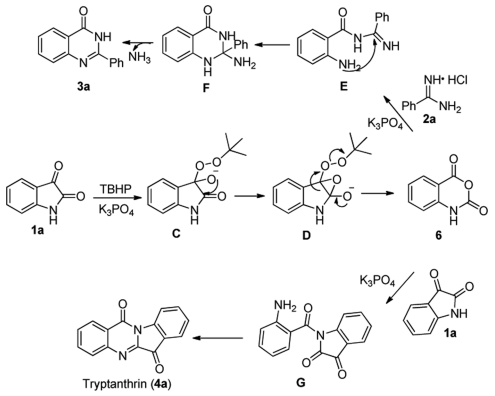
Scheme 3. Control Experiments



was treated with benzamidine hydrochloride (**2a**, 1 equiv) under the optimized conditions, 2-phenylquinazolin-4(3*H*)-one (**3a**) and tryptanthrin (**4a**) were obtained in 42% and 18% yield, respectively (Scheme 3b). When the reactions of isatin (**1a**) with TBHP (5 equiv) and K_3PO_4 (3 equiv) were conducted in DMSO at room temperature for 50 min, the target product tryptanthrin (**4a**) was also isolated in 32% yield along with the possible unstable byproducts *tert*-butyl 2-aminobenzoperoxoate detected by MS (Scheme 3c). To further demonstrate the possible isatoic anhydride intermediate implied by the aforementioned three control experiments, piperidine served as stronger electrophile to trap possible isatoic anhydride generated in situ, which gave the desired product **5** in 82% yield under standard conditions (Scheme 3d). Furthermore, when the sterically hindered 7-methylindoline-2,3-dione was conducted under the optimized conditions, only a trace of oxidative product 8-methyl-1*H*-benzo[*d*][1,3]-oxazine-2,4-dione was detected by MS (Scheme 3e). Next, when the reaction of 1*H*-benzo[*d*][1,3]oxazine-2,4-dione (**6**) and benzamidine hydrochloride (**2a**) in the presence of K_3PO_4 was performed in DMSO, the desired product **3a** was isolated in 85% yield (Scheme 3f). On the other hand, the radical scavengers, TEMPO (2,2,6,6-tetramethylpiperidinooxy) and HQ (hydroquinone), did not influence this reaction obviously (see the SI), which indicated that a radical pathway might not be involved in this reaction either. Taken together, these control experiments clearly indicated that the isatoic anhydride acted as the key intermediate involved in this domino process.

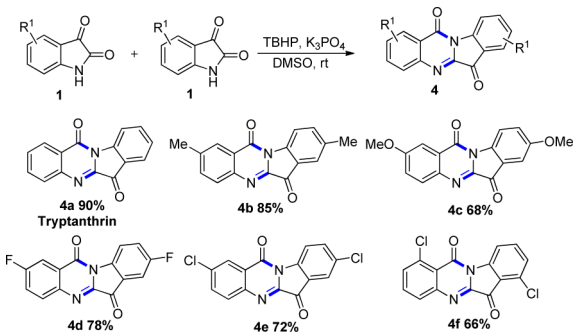
On the basis of the above observations and literature precedent,[15−17] a tentative reaction mechanism was proposed as shown in Scheme 4. Initially, the intermolecular nucleophilic attack of TBHP to isatin (**1a**) led to intermediate **C**, and intramolecular cyclization followed by rearrangement would afford the intermediate isatoic anhydride (**6**). Subsequently, the decarboxylative nucleophilic attack of isatoic anhydride (**6**) with amidine hydrochlorides (**2a**) provide the amide **E**, which was converted to the target product **3a** by deamination cyclization. In the absence of amidine hydrochlorides, self-dimerization of isatin would form tryptanthrin (**4a**) through an analogous oxidative cyclization.

Scheme 4. Possible Mechanism



To show the generality of this TBHP/K_3PO_4 system for the synthesis of tryptanthrins, several representative isatins were selected to construct symmetric tryptanthrin derivatives. Isatins containing electron-neutral (5-Me), electron-rich (5-OMe), and halogenated substituents (5-F, 5-Cl, 4-Cl) were converted to the corresponding products in moderate to good yields (Scheme 5, **4a−f**, 66−90%). To further indicate the synthetic

Scheme 5. Direct Synthesis of Tryptanthrins via a Self-Dimerization of Isatins[a,b]

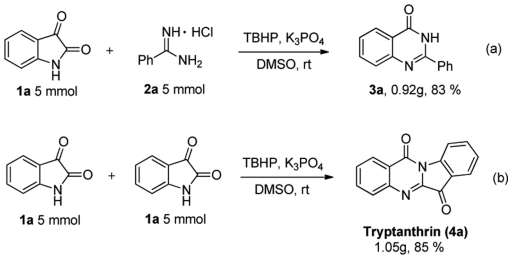


[a]Reaction conditions: **1** (1.0 mmol), TBHP (0.75 mmol), and K_3PO_4 (1.0 mmol) in DMSO (4 mL) at room temperature (25−30 °C) in a sealed vessel under air for 12 h. [b]Isolated yields.

practicality of the reaction, gram-scale syntheses of 2-phenylquinazolin-4(3*H*)-one (**3a**) and tryptanthrin (**4a**) were performed, and the desired products **3a** and **4a** were obtained in 83% and 85% yield, respectively (Scheme 6).

In summary, a synergetic TBHP/K_3PO_4-promoted domino oxidative cyclization of isatins with amidine hydrochlorides has been developed, providing a rapid access to pharmaceutically significant quinazolin-4(3*H*)-one derivatives. The advantages of

Scheme 6. Gram-Scale Experiment



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the present protocol include mild conditions, wide substrate scope, and excellent practicability. This strategy provides an elegant protocol for the concise synthesis of tryptanthrins via a rare self-dimerization of isatins under the same conditions. Further applications of this oxidative cyclization strategy for the synthesis of other fascinating heterocycles 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.6b01291.

Experimental procedures, product characterization, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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