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Iodine-Mediated C−H Functionalization of sp, sp^2, and sp^3 Carbon: A Unified Multisubstrate Domino Approach for Isatin Synthesis

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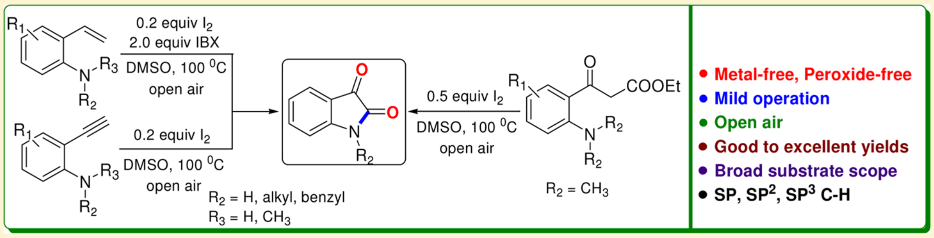
Supporting Information



ABSTRACT: Molecular iodine-promoted efficient construction of isatins from 2′-aminophenylacetylenes, 2′-aminostyrenes, and 2′-amino-β-ketoesters is developed via oxidative amidation of sp, sp^2, and sp^3 C−H bonds. The reaction involves consecutive iodination, Kornblum oxidation, and intramolecular amidation in a single reactor. The present method meets all of the atom and redox economy principles.

INTRODUCTION

Isatin is a popular pharmacophore found among many synthetic origin and natural products that displays a variety of important pharmacological and material-like properties.[1] Although its synthesis was first reported in the year 1841,[2] with the increase in advantages of modern and efficient synthetic methods for C−C and C−N bond formation,[3] several research groups have recently shown interest in making isatins. These newly devised protocols for the synthesis of isatin are based on either C−C bond formation at the ortho position of aniline with suitable precursors[4,5] or C−N bond formation of aniline with a pre-existing ortho-substituted functional group.[6−8] The former method involves the intramolecular oxidative cyclization of formyl-*N*-aryl-formamides[4] and oxidative cyclization of *N*-alkyl-2-haloacetanilides.[5] The latter involves protocols with either Cu- or I_2-mediated intramolecular oxidative C−H amidation of 2′-amino acetophenones,[6] Cu-catalyzed oxidative cyclization of arylacetamides,[7] and sulfur ylide-mediated carbonyl homologation of anthranilic acids.[8] Apart from these one pot C−C and C−N bond forming reactions, such as Cu-catalyzed oxidative acylation of secondary anilines with ethyl glyoxalate,[9] Pd-catalyzed double isonitrile insertion of 2-iodoanilines[10] and double carbonylation of anilines with CO[11] have also been developed. In addition, miscellaneous methods involving benzyne intermediates or oxidation of an indole ring have also been reported.[12,13] Although these improved protocols are found to be an improvement over conventional procedures,[14] some of the important shortcomings, such as inaccessible starting materials, harsh reaction conditions, expensive reagents, limited substrate scope, and most importantly being non-atom economic, make it necessary to develop a straightforward strategy for isatin synthesis.

The oxidation of phenylacetylenes or styrenes into highly unstable phenylglyoxals via Kornblum oxidation of in situ generated α-iodoketones has received widespread attention and is a swiftly growing field in synthetic organic chemistry. Recently, such a strategy was employed for one pot synthesis of 2-acylbenzothiazoles,[15a] 2-acyloxazoles,[15b] pyrazines,[16] quinoxalines,[16,17a] and α-ketoimides.[17b−d]

The reported methods for the synthesis of isatins from ortho-substituted anilines deal with the C−N bond formation between an electron-rich amine and an electron-accepting acid[8] or enolizable ketone;[6b,d] however, the C−N bond formation between an electron-rich amine and an electron-rich alkyne or alkene has not yet been explored. Encouraged by these studies, we envisaged that 2′-aminophenylacetylenes or 2′-aminostyrenes, which have been used for the construction of indoles,[18] can effectively be utilized for the synthesis of isatins. Herein, we present a straightforward, metal- and peroxide-free, atom economic, molecular iodine-mediated synthesis of isatins by intramolecular C−N bond formation of 2′-aminophenylacetylene (sp carbon) or 2′-aminostyrene (sp^2 carbon) as well as 2′-amino-β-ketoester (sp^3 carbon, Scheme 1).

RESULTS AND DISCUSSION

Our initial attempts focused on identifying suitable conditions for intramolecular C−N amidation between electron-rich amine and acetylene (Table 1). 2′-*N*-Benzylaminophenyl acetylene (**1a**) was identified as the model substrate, and treatment with I_2 (0.5 equiv) in DMSO at rt elicited no reaction (Table 1,

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Scheme 1. Synthesis of Isatin

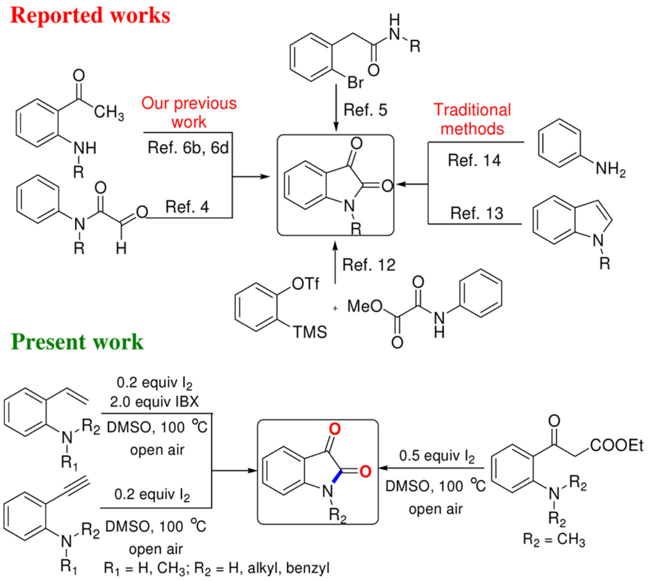
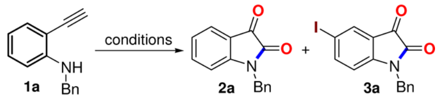


Table 1. Optimization Studies for the Formation of 2a from 2′-Aminophenylacetylene[a]



entry	catalyst (equiv)	solvent	temp (°C)	time (h)	yield of 2a/3a (%)[b]
1	I_2 (0.5)	DMSO	rt	24	nr[c]
2	I_2 (0.5)	DMSO	80	12	56/trace
3	I_2 (1.0)	DMSO	80	12	42/28
4	I_2 (0.2)	DMSO	80	10	79/0
5	I_2 (0.1)	DMSO	80	15	64/0
6	**I_2 (0.2)**	**DMSO**	**100**	**8**	**88/0**
7	I_2 (0.2)	DMSO	120	8	80/0
8	I_2 (2.0)	DMSO	100	14	0/82
9		DMSO	100	24	nd[d]
10	NIS (0.2)	DMSO	100	15	52/0
11	TBAI (0.2)	DMSO	100	20	24
12	KI (0.2)	DMSO	100	20	15
13	PIDA (0.2)	DMSO	100	20	trace
14	I_2 (0.2)	DMF	100	12	nd[d]
15	I_2 (0.2)	CH_3CN	100	12	nd[d]
16	I_2 (0.2)	toluene	100	12	nd[d]

[a] All reactions were carried out using **1a** (1.0 mmol) in solvent (3.0 mL). [b] Isolated yields. [c] No reaction (nr). [d] Not determined (nd).

entry 1). When the temperature was increased to 80 °C, C−N bond formation readily took place to provide isatin **2a** in moderate yield along with a trace amount of iodoisatin **3a** (Table 1, entry 2). Increasing the amount of I_2 (1.0 equiv) led to the formation of a mixture of **2a** and **3a** (Table 1, entry 3). Surprisingly, dropping the catalyst load to 0.2 equiv improved the yield (Table 1, entry 4) but further lowering to 0.1 equiv resulted in a decreased yield (Table 1, entry 5). Elevating the temperature to 100 °C produced the highest yield, but further increasing the temperature to 120 °C led to a low yield (Table 1, entries 6 and 7). When 2.0 equiv of I_2 was used, iodoisatin **3a** was obtained as an exclusive product in good yield (Table 1, entry 8).

No product was obtained in the absence of I_2, indicating that I_2 was crucial for this transformation (Table 1, entry 9). Among the different iodine sources, molecular iodine was found to be better for this oxidative cyclization (Table 1, entries 10−13). DMSO furnished the best yield and played a dual role as oxidizing agent and reaction medium, whereas no desired isatin was detected in other solvents (Table 1, entries 14−16). Careful analysis of the results revealed that 0.2 equiv of I_2 in DMSO at 100 °C would be the best reaction conditions for further studies.

With the optimal parameters established, the substrate scope of various 2′-aminophenylacetylenes was examined (Scheme 2). Compound **1b** with an *N*-allyl substituent offered isatin **2b** in excellent yield. The electron-donating methyl group bearing aromatic ring **1c** increased the rate of the reaction to provide isatin **2c** in excellent yield. However, the inductively electron-withdrawing -F or -Cl substituent bearing phenylacetylenes **1d** and **1e** decreased the rate of the reaction and corresponding isatins **2d** and **2e**, respectively, were obtained in good yields. Intriguingly, 2′-aminopyridyl acetylene **1f** containing a highly deactivated aromatic ring provided pyrrolopyridine-2,3-dione **2f** in good yield. The oxidation condition was so mild that the nitrogen in the pyridine ring remained unaffected.

Fascinatingly, whereas several methods fail[6b] or provide only low yield[6a,d] of isatin **2g**, the present method offers isatin **2g** from 2′-aminophenylacetylene (**1g**) in 48% yield. 2′-Acetamidophenylacetylene (**1h**), instead of providing expected *N*-acetylisatin **2h**, underwent *N*-deacetylation followed by cyclization to provide isatin **2g** in poor yield. It is interesting to note that 2′-*N*,*N*-dimethylaminophenyl acetylenes **1i**−**l** undergo tandem demethylation followed by oxidative cyclization to access corresponding isatins **2i**−**l** in good to excellent yields.[6b,d] Furthermore, 2′-secondaryaminophenylacetylenes **1a** and **1s** react with a stoichiometric amount of I_2 to provide iodoisatins **3a** and **3b**, respectively, exclusively in good yields. Similarly, 2′-*N*,*N*-dimethylaminophenylacetylene **1i** undergoes tandem demethylation, iodination, and cyclization to give iodoisatin **3c** in good yield.

Excited by these results, we next examined the feasibility of isatin formation from 2′-aminostyrenes (Table 2). To examine our hypothesis, we identified 2′-*N*-benzylaminostyrene (**4a**) as the model substrate and treated it with I_2 (1.0 equiv) and IBX (1.5 equiv) in DMSO at 80 °C (Table 2). To our pleasure, the reaction delivered isatin **2a** in 48% yield (Table 2, entry 1). Further increasing the quantity of IBX to 2.0 equiv and reducing the I_2 quantity to 0.2 equiv provided the best yield (Table 2, entries 2−5). Increasing the temperature to 120 °C led to low yield (Table 2, entry 6). Using a stoichiometric amount of I_2 played a significant role in providing iodoisatin **3a** as the major product (Table 2, entry 7). No product was detected in the absence of either I_2 or IBX, indicating that both were essential for this reaction (Table 2, entries 8 and 11). Screening other oxidants, including TBHP and H_2O_2, resulted in poor yields (Table 2, entries 9 and 10). Employing the iodine sources NIS and TBAI were not useful for the reaction (Table 2, entries 12 and 13). DMSO was more effective for obtaining isatin than other solvents (Table 2, entries 14−16). As a result, 0.2 equiv of I_2 and 2.0 equiv of IBX in DMSO at 100 °C were found to be the optimum conditions.

Under the optimal conditions described above, the substrate scope of 2′-aminostyrenes was explored, and the results are summarized in Scheme 3. As shown, compound **4b** containing an easily oxidizable *N*-allyl substituent gave isatin **2b** in 72%

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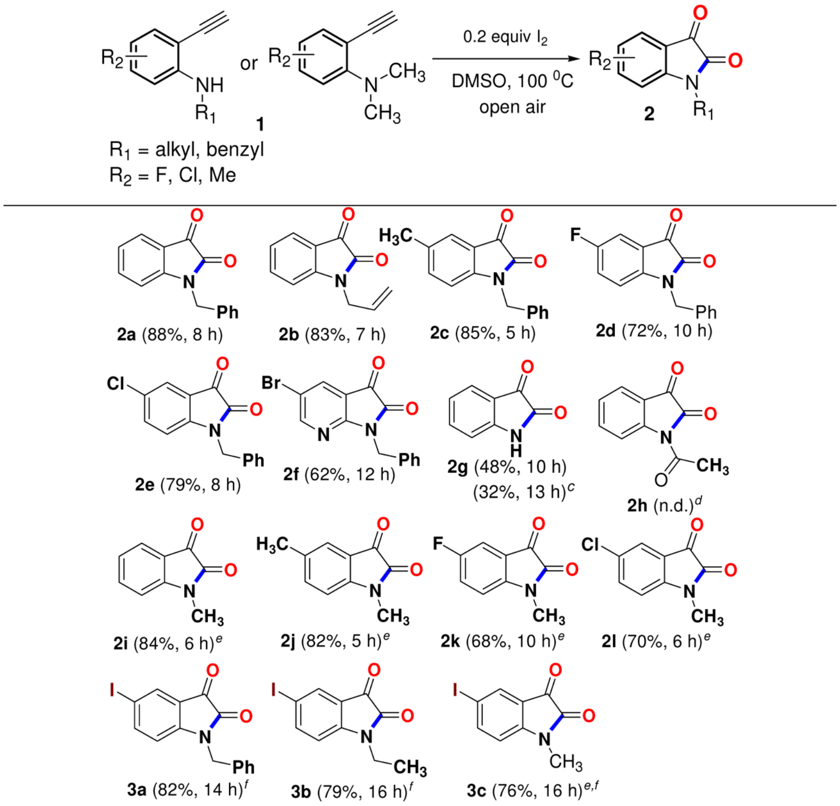
Scheme 2. Substrate Scope of 2′-Aminophenylacetylenes[a,b]



[a]Reaction conditions: **1** (1.0 mmol) and I_2 (0.2 mmol) in DMSO (3.0 mL) at 100 °C. [b]Isolated yields. [c]**1h** used as starting material. [d]Not determined. [e]Tertiary amines were used. [f]I_2 used at 2.0 mmol.

yield without any difficulty. Contrary to the failure met with the CuI/bipy system,[6a] the present method remarkably accomplished the conversion of *N*-ethyl acetate-substituted 2′-aminostyrene **4m** to isatin **2m** in good yield.

Similarly, 2′-*N*-(2-bromoethyl)-aminostyrene **4n** produced isatin **2n** in good yield. The electronic nature of the substituent's aromatic ring showed significant influence on the rate of the reaction. Whereas the electron-donating -OMe group of **4o** increased the rate of the reaction, inductively electron-withdrawing -F and -Br substituents of **4d** and **4p** decreased the rate. Regardless of the electronic nature of the substituents, isatins **2o**, **2d**, and **2p** were obtained in good yields. 2′-*N*,*N*-Dialkylamine-substituted styrenes **4i**, **4k**, **4q**, and **4r** underwent tandem demethylation and cyclization to produce the corresponding isatins **2i**, **2k**, **2q**, and **2r** in good to excellent yield. Unsubstituted 2′-aminostyrene **4g** resulted in isatin **2g** in less yield. Similar to earlier observations, *N*-acetyl 2′-aminostyrene **4h** produced isatin **2g** instead of the expected isatin **2h**, albeit in low yield. Significantly, with a stoichiometric amount of I_2, compound **4a** produced iodoisatin **3a** in good yield.

With excitement, we next considered the C−N bond formation between the amine and sp^3 carbon of 2′-aminoethylbenzoylacetate (Scheme 4). The reaction of **5a** with 0.5 equiv of I_2 in DMSO at 100 °C furnished isatin **2i** in 66% isolated yield via N-demethylation[18c] and the Krapcho dealkoxycarbonylation process.[19] To the best of our knowledge, this is the first time a Krapcho dealkoxycarbonylation was observed in the presence of molecular iodine. Under the same reaction conditions, compounds **5b**, **5c**, and **5d** gave corresponding isatins **2r**, **2s**, and **3c**, respectively, in moderate yields.

Further, to demonstrate the synthetic utility of the present method, we converted compound **1a** to isatin **2a** under optimal condition and subsequently treated **2a** with thiosemicarbazide (**8**) to get antiviral agent drug metisazone (**9**) in high yield in one pot (Scheme 5). Interestingly, here, I_2 facilitated the coupling of in situ formed isatin **2a** with thiosemicarbazide (**8**) at rt by avoiding harsh conditions.[20] Next, we conducted the synthesis of anticonvulsant agent **7** as a direct two-step method without purification of the isatin **2i** intermediate, and the desired product was obtained in 84% yield, which shows the high efficiency of the present synthetic method (Scheme 5).

On the basis of earlier reports and present observations, we herein propose a plausible mechanism for the formation of isatin **2** (Scheme 6). Substrates **1** and **4** on iodination give α-iodoketone **A**,[16,17] which can readily be converted to phenylglyoxal **B** by Kornblum oxidation in the presence of DMSO.[21] Further activation of the formyl group of phenylglyoxal **B** by Lewis acidic I_2 (**C**)[22] facilitates nucleophilic addition of the ortho amine group to form secondary alcohol **D**. Substrate **5** initially underwent cyclization to give oxindole salt, which further loses its methyl group by highly nucleophilic iodide ions to generate oxindole **E**.[18c] Next, oxindole **E** underwent Krapcho dealkoxycarbonylation to give secondary alcohol **D**.[19] Secondary alcohol **D** then underwent self-oxidation to provide isatin **2**. Two moles of HI released in the reaction reacted with DMSO to regenerate I_2.

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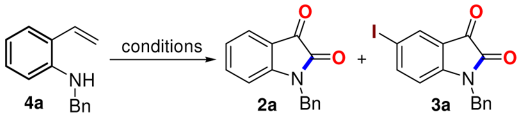
Table 2. Optimization Studies for the Formation of 2a from 2′-Aminostyrene[a]



entry	catalyst (equiv)	oxidant (equiv)	solvent	temp (°C)	time (h)	yield of 2a/3a(%)[b]
1	I_2 (1.0)	IBX (1.5)	DMSO	80	16	48/12
2	I_2 (1.0)	IBX (2.0)	DMSO	80	15	53/16
3	I_2 (0.2)	IBX (2.0)	DMSO	80	18	71/0
4	I_2 (0.1)	IBX (2.0)	DMSO	80	18	60/0
5	**I_2 (0.2)**	**IBX (2.0)**	**DMSO**	**100**	**12**	**78/0**
6	I_2 (0.2)	IBX (2.0)	DMSO	120	10	72/0
7	I_2 (2.0)	IBX (2.0)	DMSO	100	20	6/63
8	I_2 (0.2)		DMSO	100	24	nd[c]
9	I_2 (0.2)	TBHP (2.0)	DMSO	100	20	26/0
10	I_2 (0.2)	H_2O_2 (2.0)	DMSO	100	20	18/0
11		IBX (2.0)	DMSO	100	20	nd[c]
12	NIS (0.2)	IBX (2.0)	DMSO	100	20	34/0
13	TBAI (0.2)	IBX (2.0)	DMSO	100	20	nd[c]
14	I_2 (0.2)	IBX (2.0)	DMF	100	18	nd[c]
15	I_2 (0.2)	IBX (2.0)	toluene	100	18	nd[c]
16	I_2 (0.2)	IBX (2.0)	CH_3CN	100	18	nd[c]

[a] All reactions were carried out using **4a** (1.0 mmol) in solvent (3.0 mL). [b] Isolated yield. [c] Not determined (nd).

CONCLUSION

In conclusion, we developed a molecular iodine-promoted domino synthesis of isatins from easily accessible 2′-aminophenylacetylenes, 2′-aminostyrenes, and 2′-amino-*β*-ketoesters via C−H functionalization of sp, sp^2, and sp^3 carbons. The present method is applicable to primary, secondary, and tertiary amines and amides. It involves sequential iodination, Kornblum oxidation, and intramolecular nucleophilic addition in a single pot. The I_2 catalytic system was found to be useful in the one pot synthesis of antiviral drug Metisazone. The present method is mild and avoids metal, bases, and peroxide. It is highly atom economic and very lucrative in organic and medicinal chemistry because isatins are valuable synthetic intermediates for bioactive compounds.

EXPERIMENTAL SECTION

General Information. All reagents were purchased commercially and used without further purification. ^{1}H and ^{13}C NMR were recorded with a 400 MHz spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ and DMSO with tetramethylsilane as the internal standard. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad resonance. All the NMR spectra were acquired at ambient temperature. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and staining with I_2 on silica gel. High resolution mass spectra were recorded on a Q-TOF analyzer.

General Method A: Typical Experimental Procedure for the Synthesis of Isatins from 2′-Aminophenylacetylenes. To a solution of (2-ethynyl-phenyl)-alkyl-amine (**1**, 1.0 equiv) in DMSO was added I_2 (0.2 equiv) at ambient temperature; the mixture was then heated at 100 °C under an air atmosphere, and progress of the reaction was monitored by TLC. Upon completion, the mixture was allowed to cool to ambient temperature and quenched with aq sodium thiosulfate and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent.

General Method B: Typical Experimental Procedure for the Synthesis of Isatins from 2′-Aminostyrenes. To a solution of alkyl-(2-vinyl-phenyl)-amine (**4**, 1.0 equiv) in DMSO were added I_2 (0.2 equiv) and IBX (2.0 equiv), and the mixture was then stirred at ambient temperature for 3 h under an air atmosphere. After 3 h, the reaction temperature was raised to 100 °C, and progress of the reaction was monitored by TLC. Upon completion, the mixture was allowed to cool to ambient temperature and quenched with aq sodium thiosulfate and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent.

General Method C: Typical Experimental Procedure for the Synthesis of Isatins from 2′-Amino-*β*-ketoesters. To a solution of 3-(2-dimethylamino-phenyl)-3-oxo-propionic acid ethyl ester (**5**, 1.0 equiv) in DMSO was added I_2 (0.5 equiv) at ambient temperature; the mixture was then heated at 100 °C under an air atmosphere, and progress of the reaction was monitored by TLC. Upon completion, the mixture was allowed to cool to ambient temperature and quenched with aq sodium thiosulfate and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent.

*1-Benzyl-1H-indole-2,3-dione (**2a**).*[4] The reaction was carried out according to general method A using benzyl-(2-ethynyl-phenyl)-amine (**1a**, 100 mg, 0.482 mmol), I_2 (24.5 mg, 0.096 mmol), and DMSO (3 mL). Conditions: 100 °C, 8 h. Title compound **2a** (100.7 mg, 88% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Alternatively, the reaction was carried out according to general method B using benzyl-(2-vinyl-phenyl)-amine (**4a**, 100 mg, 0.477 mmol), IBX (267.6 mg, 0.995 mmol), I_2 (24.2 mg, 0.095 mmol), and DMSO (3 mL). Conditions: 100 °C, 12 h. Title compound **2a** (88.4 mg, 78% yield) was obtained as a red solid.

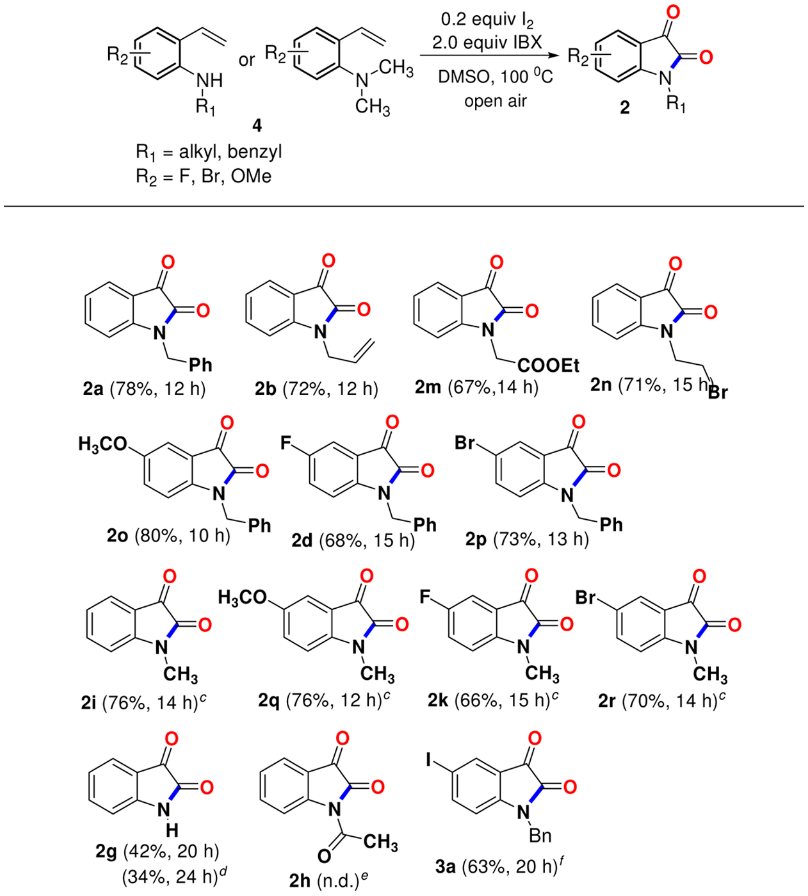
Mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.33−7.25 (m, 5H), 7.06 (t, J = 7.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 158.3, 150.7, 138.5, 134.6, 129.0, 128.2, 127.5, 125.3, 123.9, 117.6, 111.1, 44.0.

*1-Allyl-1H-indole-2,3-dione (**2b**).*[23] The reaction was carried out according to general method A using allyl-(2-ethynyl-phenyl)-amine (**1b**, 100 mg, 0.636 mmol), I_2 (32.3 mg, 0.127 mmol), and DMSO (3 mL). Conditions: 100 °C, 7 h. Title compound **2b** (98.8 mg, 83% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.55 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.90−5.80 (m, 1H), 5.35−5.28 (m, 2H), 4.38−4.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 157.9, 150.8, 138.3, 130.3, 125.4, 123.8, 118.6, 117.6, 110.9, 42.5.

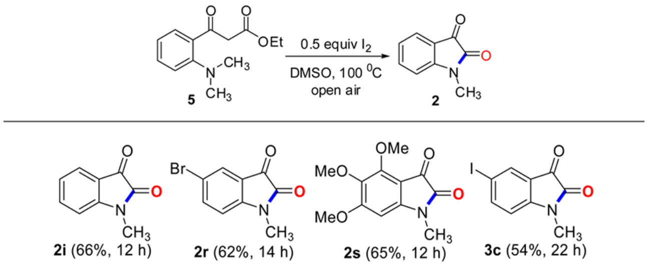
Alternatively, the reaction was carried out according to general method B using allyl-(2-vinyl-phenyl)-amine (**4b**, 100 mg, 0.628 mmol), IBX (351.7 mg, 1.256 mmol), I_2 (31.9 mg, 0.125 mmol), and DMSO (3 mL). Conditions: 100 °C, 12 h. Title compound **2b** (84.6 mg, 72% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Scheme 3. Substrate Scope of 2′-Aminostyrenes[a,b]



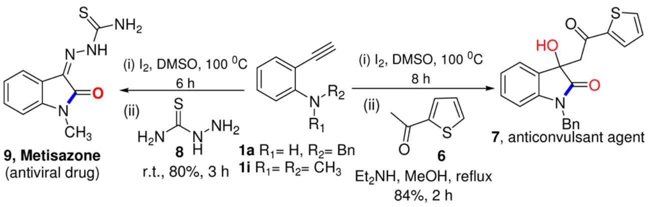
[a]Reaction conditions: **4** (1.0 mmol), I_2 (0.2 mmol), and IBX (2.0 mmol) in DMSO (3.0 mL) at 100 °C. [b]Isolated yields. [c]Tertiary amines were used. [d]**1h** used as starting material. [e]Not determined (nd). [f]Used I_2 at 2.0 mmol.

Scheme 4. Synthesis of Isatins from 2′-Amino-β-Ketoesters[a,b]



[a]Reaction conditions: **5** (1.0 mmol) and I_2 (0.5 mmol) in DMSO (3.0 mL) at 100 °C. [b]Isolated yields.

Scheme 5. Telescoped Synthesis of Bioactive Isatin Compounds



5-Methyl-1-benzyl-1H-indole-2,3-dione (**2c**).[6e] The reaction was carried out according to general method A using benzyl-(2-ethynyl-4-methyl-phenyl)-amine (**1c**, 100 mg, 0.451 mmol), I_2 (22.9 mg, 0.09 mmol), and DMSO (3 mL). Conditions: 100 °C, 5 h. Title compound **2c** (96.5 mg, 85% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39−7.29 (m, 6H), 6.68 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 158.4, 148.5, 138.7, 134.7, 133.7, 129.0, 128.1, 127.4, 125.7, 117.7, 110.8, 44.0, 20.6.

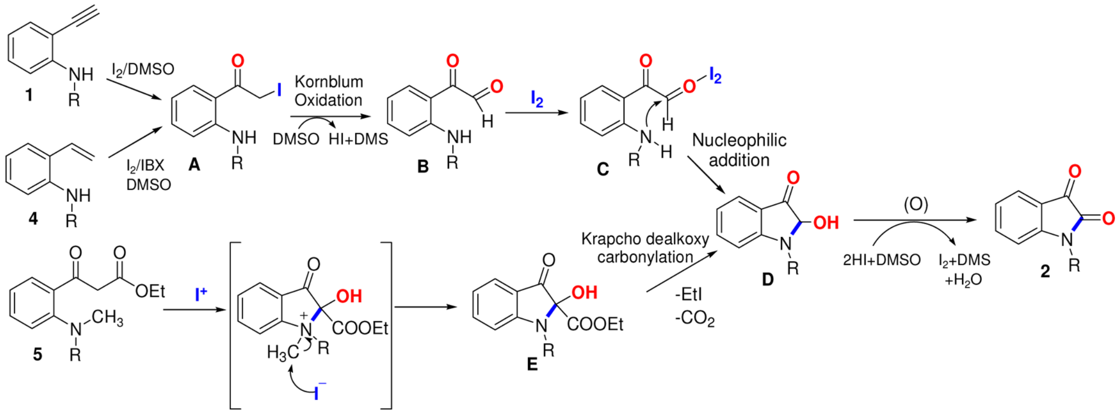
5-Fluoro-1-benzyl-1H-indole-2,3-dione (**2d**). The reaction was carried out according to general method A using benzyl-(2-ethynyl-4-fluoro-phenyl)-amine (**1d**, 100 mg, 0.444 mmol), I_2 (22.5 mg, 0.088 mmol), and DMSO (3 mL). Conditions: 100 °C, 10 h. Title compound **2d** (81.5 mg, 72% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.18 (m, 6H), 7.11 (td, J = 2.4, 2.8, 2.8 Hz, 1H), 6.66 (dd, J = 3.6, 3.6 Hz, 1H), 4.83 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 160.6, 158.1, 158.1, 146.8, 134.2, 129.1, 128.3, 127.4, 124.8, 124.6, 118.3, 118.2, 112.5, 112.3, 112.3, 44.2. HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{10}FNNaO_2$ 278.0593, found 278.0587.

Alternatively, the reaction was carried out according to general method B using benzyl-(4-fluoro-2-vinyl-phenyl)-amine (**4d**, 100 mg, 0.439 mmol), IBX (246.4 mg, 0.879 mmol), I_2 (22.3 mg, 0.087 mmol), and DMSO (3 mL). Conditions: 100 °C, 15 h. Title compound **2d** (76.3 mg, 68% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

5-Chloro-1-benzyl-1H-indole-2,3-dione (**2e**).[24] The reaction was carried out according to general method A using benzyl-(4-chloro-2-ethynyl-phenyl)-amine (**1e**, 100 mg, 0.413 mmol), I_2 (21.0 mg, 0.082 mmol), and DMSO (2 mL). Conditions: 100 °C, 8 h. Title compound

Scheme 6. Proposed Mechanism for the Formation of 2



2e (88.8 mg, 79% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 135−136 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (d, J = 2.0 Hz, 1H), 7.36 (dd, J = 8.4, 2.0 Hz, 1H), 7.30−7.23 (m, 5H), 6.65 (d, J = 8.4 Hz, 1H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.3, 157.7, 148.9, 137.7, 134.0, 129.8, 129.2, 128.4, 127.4, 125.3, 118.5, 112.3, 44.2.

1-Benzyl-5-bromo-1H-pyrrolo(2,3-b)pyridine-2,3-dione ***(2f)***. The reaction was carried out according to general method A using benzyl-(5-bromo-3-ethynyl-pyridin-2-yl)-amine) (**1f**, 100 mg, 0.348 mmol), I$_2$ (17.7 mg, 0.069 mmol), and DMSO (3 mL). Conditions: 100 °C, 12 h. Title compound **2f** (68.4 mg, 62% yield) was obtained as a light yellow solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 156−158 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.43 (d, J = 2.0 Hz, 1H), 7.80 (t, J = 1.2 Hz, 1H), 7.39−7.37 (m, 2H), 7.25−7.17 (m, 3H), 4.90 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 180.9, 161.7, 157.5, 156.3, 135.2, 135.1, 128.9, 128.8, 128.3, 115.2, 112.9, 42.8. HRMS (ESI) m/z [M + Na]$^+$ calcd for C$_{14}$H$_9$BrN$_2$NaO$_2$ 338.9745, found 338.9763.

1H-Indole-2,3-dione ***(2g)***. The reaction was carried out according to general method A using 2-ethynyl-phenyl-amine (**1g**, 100 mg, 0.853 mmol), I$_2$ (43.3 mg, 0.17 mmol), and DMSO (3 mL). Conditions: 100 °C, 10 h. Title compound **2g** (60.2 mg, 48% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 194−196 °C; ^{1}H NMR (300 MHz, CDCl$_3$ + DMSO) δ 10.04 (d, J = 12.6 Hz, 1H), 6.67−6.61 (m, 2H), 6.20−6.14 (m, 1H), 6.04 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$ + DMSO) δ 189.5, 164.4, 155.9, 143.3, 129.8, 127.9, 122.5, 117.4. Compound **2g** is commercially available.

Alternatively, the reaction was carried out according to general method A using *N*-(2-ethynyl-phenyl)-acetamide (**1h**, 100 mg, 0.628 mmol), I$_2$ (31.9 mg, 0.125 mmol), and DMSO (3 mL). Conditions: 100 °C, 13 h. Title compound **2g** (29.6 mg, 32% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Alternatively, the reaction was carried out according to general method B using 2-vinyl-phenyl-amine (**4g**, 100 mg, 0.839 mmol), IBX (470.0 mg, 1.678 mmol), I$_2$ (42.6 mg, 0.167 mmol), and DMSO (3 mL). Conditions: 100 °C, 20 h. Title compound **2g** (51.8 mg, 42% yield) was obtained as a red solid.

Alternatively, the reaction was carried out according to general method B using 2-vinyl-phenyl-amine (**4g**, 100 mg, 0.620 mmol), IBX (347.4 mg, 1.240 mmol), I$_2$ (31.5 mg, 0.124 mmol), and DMSO (3 mL). Conditions: 100 °C, 24 h. Title compound **2g** (31.0 mg, 34% yield) was obtained as a red solid.

1-Methyl-1H-indole-2,3-dione ***(2i)***.[24] The reaction was carried out according to general method A using (2-ethynyl-phenyl)-dimethyl-amine (**1i**, 100 mg, 0.688 mmol), I$_2$ (34.9 mg, 0.137 mmol), and DMSO (3 mL). Conditions: 100 °C, 6 h. Title compound **2i** (93.2 mg, 84% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 121−122 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55−7.47 (m, 2H), 7.04 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 183.4, 158.2, 151.4, 138.6, 125.1, 123.8, 117.3, 110.1, 26.2.

Alternatively, the reaction was carried out according to general method B using dimethyl-(2-vinyl-phenyl)-amine (**4i**, 100 mg, 0.679 mmol), IBX (380.4 mg, 1.358 mmol), I$_2$ (34.5 mg, 0.135 mmol), and DMSO (3 mL). Conditions: 100 °C, 14 h. Title compound **2i** (83.2 mg, 76% yield) was obtained as a red solid.

Alternatively, the reaction was carried out according to general method C using 3-(2-dimethylamino-phenyl)-3-oxo-propionic acid ethyl ester (**5a**, 100 mg, 0.425 mmol), I$_2$ (53.9 mg, 0.212 mmol), and DMSO (2 mL). Conditions: 100 °C, 12 h. Title compound **2i** (45.2 mg, 66% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

5-Methyl-1-methyl-1H-indole-2,3-dione ***(2j)***.[6e] The reaction was carried out according to general method A using (2-ethynyl-4-methyl-phenyl)-dimethyl-amine (**1j**, 100 mg, 0.628 mmol), I$_2$ (31.9 mg, 0.125 mmol), and DMSO (3 mL). Conditions: 100 °C, 5 h. Title compound **2j** (90.2 mg, 82% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 157−159 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.14 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 183.6, 158.4, 149.3, 138.8, 133.7, 125.6, 117.4, 109.8, 26.2, 20.7.

5-Fluoro-1-methyl-1H-indole-2,3-dione ***(2k)***.[5] The reaction was carried out according to general method A using (2-ethynyl-4-fluoro-phenyl)-dimethyl-amine (**1k**, 100 mg, 0.612 mmol), I$_2$ (31.1 mg, 0.122 mmol), and DMSO (3 mL). Conditions: 100 °C, 10 h. Title compound **2k** (74.6 mg, 68% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Alternatively, the reaction was carried out according to general method B using (4-fluoro-2-vinyl-phenyl)-dimethyl-amine (**4k**, 100 mg, 0.605 mmol), IBX (339.0 mg, 1.21 mmol), I$_2$ (30.7 mg, 0.121 mmol), and DMSO (3 mL). Conditions: 100 °C, 15 h. Title compound **2k** (71.5 mg, 66% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 160−162 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28−7.20 (m, 2H), 6.82−6.79 (m, 1H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.8, 160.0, 158.1, 158.0, 147.5, 124.8, 124.6, 118.0, 117.9, 112.4, 112.2, 111.2, 111.1, 26.3.

5-Chloro-1-methyl-1H-indole-2,3-dione ***(2l)***.[25] The reaction was carried out according to general method A using (4-chloro-2-ethynyl-phenyl)-dimethyl-amine (**1l**, 100 mg, 0.556 mmol), I$_2$ (28.2 mg, 0.111 mmol), and DMSO (3 mL). Conditions: 100 °C, 6 h. Title compound **2l** (76.2 mg, 70% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 156–159 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59–7.57 (m, 2H), 6.87–6.85 (m, 1H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.3, 157.7, 149.7, 137.7, 129.7, 125.3, 118.3, 111.2, 26.4.

*Ethyl 2-(2,3-Dioxoindolin-1-yl)acetate (**2m**).*[26] The reaction was carried out according to general method B using (2-vinyl-phenyl-amino)-acetic acid ethyl ester (**4m**, 100 mg, 0.487 mmol), IBX (272.8 mg, 0.974 mmol), I$_2$ (24.7 mg, 0.097 mmol), and DMSO (3 mL). Conditions: 100 °C, 14 h. Title compound **2m** (76.1 mg, 67% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 125–128 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65–7.57 (m, 2H), 7.16 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.49 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.5, 166.8, 158.1, 150.3, 138.4, 125.6, 124.2, 117.7, 110.1, 62.2, 41.3, 14.1.

*1-(2-Bromoethyl)indoline-2,3-dione (**2n**).*[26] The reaction was carried out according to general method B using (2-bromo-ethyl)-(2-vinyl-phenyl)-amine (**4n**, 100 mg, 0.442 mmol), IBX (247.6 mg, 0.884 mmol), I$_2$ (22.4 mg, 0.088 mmol), and DMSO (3 mL). Conditions: 100 °C, 15 h. Title compound **2n** (79.7 mg, 71% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 132–134 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65–7.59 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.0 (d, J = 7.6 Hz, 1H), 4.15 (t, J = 6.8 Hz, 2H), 3.61 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.6, 158.2, 150.5, 138.4, 125.7, 124.1, 117.7, 110.2, 42.0, 27.1.

*1-Benzyl-5-methoxy-1H-indole-2,3-dione (**2o**).* The reaction was carried out according to general method B using benzyl-(4-methoxy-2-vinyl-phenyl)-amine (**4o**, 100 mg, 0.417 mmol), IBX (234.0 mg, 0.835 mmol), I$_2$ (21.2 mg, 0.083 mmol), and DMSO (3 mL). Conditions: 100 °C, 10 h. Title compound **2o** (89.3 mg, 80% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 122–124 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25–7.17 (m, 5H), 7.01–6.99 (m, 1H), 6.93–6.90 (m, 1H), 6.59 (d, J = 8.8 Hz, 1H), 4.78 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 183.6, 158.4, 156.5, 144.5, 134.6, 129.0, 128.1, 127.4, 124.6, 118.1, 112.1, 109.6, 55.9, 44.0. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{14}NO_3$ 268.0974, found 268.0976.

*5-Bromo-1-benzyl-1H-indole-2,3-dione (**2p**).*[27] The reaction was carried out according to general method B using benzyl-(4-bromo-2-vinyl-phenyl)-amine (**4p**, 100 mg, 0.347 mmol), IBX (194.3 mg, 0.694 mmol), I$_2$ (17.6 mg, 0.069 mmol), and DMSO (3 mL). Conditions: 100 °C, 13 h. Title compound **2p** (80.0 mg, 73% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 147–149 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 (d, J = 2.0 Hz, 1H), 7.58 (dd, J = 8.4, 2.0 Hz, 1H), 7.37–7.29 (m, 5H), 6.67 (d, J = 8.4 Hz, 1H), 4.92 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.0, 157.5, 149.4, 140.5, 134.0, 129.2, 128.4, 128.2, 127.4, 118.9, 116.8, 112.7, 44.2.

*5-Methoxy-1-methyl-1H-indole-2,3-dione (**2q**).*[5] The reaction was carried out according to general method B using (4-methoxy-2-vinyl-phenyl)-dimethyl-amine (**4q**, 100 mg, 0.564 mmol), IBX (316.0 mg, 1.128 mmol), I$_2$ (28.6 mg, 0.112 mmol), and DMSO (3 mL). Conditions: 100 °C, 12 h. Title compound **2q** (82.0 mg, 76% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 177–178 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09–7.03 (m, 2H), 6.74 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 183.7, 158.3, 156.6, 145.3, 124.5, 117.8, 110.9, 109.6, 56.0, 26.2.

*5-Bromo-1-methyl-1H-indole-2,3-dione (**2r**).*[28] The reaction was carried out according to general method B using (4-bromo-2-vinyl-phenyl)-dimethyl-amine (**4r**, 100 mg, 0.442 mmol), IBX (247.6 mg, 0.884 mmol), I$_2$ (22.4 mg, 0.088 mmol), and DMSO (3 mL). Conditions: 100 °C, 14 h. Title compound **2r** (74.3 mg, 70% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Alternatively, the reaction was carried out according to general method C using 3-(5-bromo-2-dimethylamino-phenyl)-3-oxo-propionic acid ethyl ester (**5b**, 100 mg, 0.318 mmol), I$_2$ (40.4 mg, 0.159 mmol), and DMSO (3 mL). Conditions: 100 °C, 14 h. Title compound **2r** (47.3 mg, 62% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 174–177 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (d, J = 1.6 Hz, 2H), 7.71 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.1, 157.5, 150.1, 140.6, 128.1, 118.6, 116.7, 111.6, 26.3.

*1-Methyl-4,5,6-trimethoxy-1H-indole-2,3-dione (**2s**).*[6b] The reaction was carried out according to general method C using 3-(6-dimethylamino-2,3,4-trimethoxy-phenyl)-3-oxo-propionic acid ethyl ester (**5c**, 100 mg, 0.307 mmol), I$_2$ (39.0 mg, 0.153 mmol), and DMSO (3 mL). Conditions: 100 °C, 12 h. Title compound **2s** (50.2 mg, 65% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 108–110 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.11 (s, 1H), 4.21 (s, 3H), 4.00 (s, 3H), 3.77 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 176.7, 161.3, 158.2, 153.3, 148.5, 135.4, 101.3, 88.3, 88.3, 61.3, 60.5, 55.8, 55.7, 28.7, 25.2.

*5-Iodo-1-benzyl-1H-indole-2,3-dione (**3a**).*[29] The reaction was carried out according to general method A using benzyl-(2-ethynyl-phenyl)-amine (**1a**, 100 mg, 0.482 mmol), I$_2$ (245.0 mg, 0.964 mmol), and DMSO (3 mL). Conditions: 100 °C, 14 h. Title compound **3a** (143.6 mg, 82% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 152–154 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (s, 1H), 7.76 (dd, J = 8.4, 1.6 Hz, 1H), 7.37–7.29 (m, 5H), 6.57 (d, J = 8.0 Hz, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 181.9, 157.2, 150.0, 146.3, 134.0, 133.9, 129.2, 128.4, 127.4, 119.2, 113.1, 86.2, 44.1.

Alternatively, the reaction was carried out according to general method B using benzyl-(2-vinyl-phenyl)-amine (**4a**, 100 mg, 0.477 mmol), IBX (267.6 mg, 0.955 mmol), I$_2$ (242.5 mg, 0.955 mmol), and DMSO (3 mL). Conditions: 100 °C, 20 h. Title compound **3a** (109.3 mg, 63% yield) was obtained as a red solid.

*5-Iodo-1-ethyl-1H-indole-2,3-dione (**3b**).*[29] The reaction was carried out according to general method A using ethyl-(2-ethynyl-phenyl)-amine (**1s**, 100 mg, 0.688 mmol), I$_2$ (350 mg, 1.377 mmol), and DMSO (3 mL). Conditions: 100 °C, 16 h. Title compound **3b** (163.8 mg, 79% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 140–143 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.90–7.87 (m, 2H), 6.72 (d, J = 8.8 Hz, 1H), 3.77 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 182.3, 156.9, 150.0, 146.3, 134.0, 119.2, 112.1, 85.8, 35.1, 12.4.

*5-Iodo-1-methyl-1H-indole-2,3-dione (**3c**).*[29] The reaction was carried out according to general method A using methyl-(2-ethynyl-phenyl)-amine (**1i**, 100 mg, 0.762 mmol), I$_2$ (387 mg, 1.524 mmol), and DMSO (3 mL). Conditions: 100 °C, 16 h. Title compound **3c** (166.3 mg, 76% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Alternatively, the reaction was carried out according to general method C using 3-(2-dimethylamino-5-iodo-phenyl)-3-oxo-propionic acid ethyl ester (**5d**, 100 mg, 0.276 mmol), I$_2$ (35.1 mg, 0.138 mmol), and DMSO (3 mL). Conditions: 100 °C, 22 h. Title compound **3c** (42.9 mg, 54% yield) was obtained as a red solid after passing through a short silica gel column (hexane/ethyl acetate, 9:1).

Mp 160–162 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92–7.87 (m, 2H), 6.71 (d, J = 8.4 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 181.9, 157.2, 150.7, 146.4, 133.7, 119.0, 112.0, 86.0, 26.3.

*1-Benzyl-3-hydroxy-3-(2-oxo-2-thiophen-2-yl-ethyl)-1,3-dihydro-indol-2-one (**7**).* To a solution of benzyl-(2-ethynyl-phenyl)-amine (**1a**, 100 mg, 0.482 mmol) were added I$_2$ (24.5 mg, 0.096 mmol) and DMSO (3 mL) at ambient temperature, and the mixture was then heated at 100 °C under an air atmosphere. After 8 h, the reaction mixture was cooled to ambient temperature and quenched with sodium thiosulfate water and ethyl acetate. After drying over Na$_2$SO$_4$ and being evaporated, the crude product was dissolved in EtOH (3 mL), 2-acetyl thiophene (**6**, 67.0 mg, 0.530 mmol) and Et$_2$NH (3 to 4 drops) were then added at ambient temperature and heated at reflux for 2 h. Upon completion, the reaction mixture was cooled to ambient temperature and diluted with water and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (7:3) as eluent. Title compound **7** (147.3 mg, 84% yield) was obtained as a colorless solid.

Mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 4.0 Hz, 1H), 7.51 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.25−7.12 (m, 5H), 7.05 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 4.4 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 4.88 (s, 1H), 4.80 (q, J = 24.0 Hz, 2H), 3.69 (d, J = 16.4 Hz, 1H), 3.48 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 176.8, 143.6, 142.9, 135.5, 134.9, 133.2, 129.9, 129.8, 128.9, 128.4, 127.7, 127.3, 124.1, 123.2, 109.8, 74.5, 45.4, 44.0. HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{17}NNaO_3S$ 386.0827, found 386.0836.

*Metisazone (**9**).*[30] To a solution of (2-ethynyl-phenyl)-dimethyl-amine (**1i**, 100 mg, 0.688 mmol) were added I_2 (34.9 mg, 0.137 mmol) and DMSO (3 mL) at ambient temperature, and the mixture was then heated at 100 °C under an air atmosphere. After 6 h, the reaction mixture was cooled to ambient temperature, and then thiosemicarbazide (**8**, 69.0 mg, 0.757 mmol) was added and stirred for 3 h. After 3 h, the reaction mixture was quenched with sodium thiosulfate water and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent. Title compound **9** (129.0 mg, 80% yield) was obtained as a yellow solid.

Mp 223−225 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.36 (s, 1H), 9.05 (s, 1H), 8.66 (s, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 178.7, 160.6, 143.5, 131.1, 131.0, 122.8, 120.5, 119.2, 109.7, 25.6.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00581.

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Notes

The authors declare no competing financial interest.

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