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Direct Amidation of 2′-Aminoacetophenones Using I_2-TBHP: A Unimolecular Domino Approach toward Isatin and Iodoisatin

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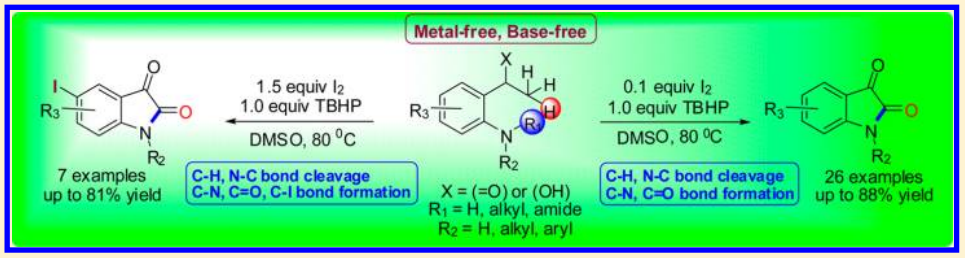
Supporting Information



ABSTRACT: Synthesis of isatin and iodoisatin from 2′-aminoacetophenone was achieved via oxidative amido cyclization of the sp^3 C−H bond using I_2−TBHP as the catalytic system. The reaction proceeds through sequential iodination, Kornblum oxidation, and amidation in one pot. This method is simple, atom economic, and works under metal- and base-free conditions.

INTRODUCTION

Domino reactions are widely employed in organic synthesis due to high atom economy, minimum waste generation, and construction of complex molecules through two or more bond formations in one pot.[1] Recently, the focus has been on application of unimolecular domino reactions for the construction of frameworks which are hitherto difficult.[2] Since toxic and expensive metal catalysts[3] are used, the advantages of domino reaction are overshadowed, and hence, the development of environmentally benign domino process become highly desirable.

The isatin skeleton is ubiquitous and found among scores of natural products,[4] synthetic intermediates,[5] and bioactive compounds.[6] The versatility of isatin as a synthetic intermediate is due to the reactivity of N(1)−H,[7] C(3)=O,[8] and aromatic C−H functional groups. Because of its extensive application as a crucial chemical block, different methods, based on inter- and intramolecular reactions, were reported. The intermolecular approaches include regioselective *ortho* acylation of anilines with suitable carbonyl precursors,[9a] Pd-catalyzed double carbonylation of 2-haloanilides,[9b] CsF-mediated reaction of arynes with methyl 2-oxo-2-(arylamino)acetates (Scheme 1, eq 1),[9c] and ylide-mediated carbonyl homologation and oxidation of anthranilic acid (Scheme 1, eq 2).[9d] However, these procedures are associated with some drawbacks, such as harsh conditions,[9a] use of expensive Pd catalyst,[9b] nonregioselective, limited substrate scope, and most importantly, non-atom economy as only a part of the reagent used for the introduction of carbonyl group is retained.[9] To overcome the regioselective and atom-economic issues, a few novel unimolecular domino procedures have been developed recently. These are $CeCl_3 \cdot 7H_2O$/IBX-promoted oxidation of 3-alkylindoles,[10a] Pd-catalyzed annulation of 2-(2-haloethynyl)-1-nitrobenzenes,[10b] $CuCl_2$-catalyzed oxidative acylation of formyl-*N*-arylformamides,[10c] CuI-promoted cyclization of 2-bromoarylacetamides[10d] and CuI-,[10e] or $Cu(OAc)_2 \cdot H_2O$-,[10f] or SeO_2-mediated[10g] oxidative amidation of 2′-*N*-alkyl/arylaminoacetophenones. The need for inaccessible starting materials,[10b−d] high boiling solvent (140 °C),[10e] and harmful reagents such as SeO_2[10g] makes these methods still less attractive. In addition, some of the methods either failed[10e−g] or did not study the acetophenones with 2′-NH_2 or 2′-*N*-amido and 2′-tertiary aniline groups.[10f]

On the other hand, iodoisatins are important intermediates and frequently used in the synthesis of bioactive arylanthranilic acids.[11] There are only few isolated reports on the synthesis of iodoisatins using special reagents such as $KICl_2$−H_2O, 2 days,[12] ICl−MeOH, 5 h,[13] IPy_2BF_4−CF_3COOH, 40 min,[14] and NIS−TfOH,[15] usually under strong acidic conditions. Thus, there is a significant need to develop a versatile, convenient, and economic method for the synthesis of isatin derivatives.

In the presence of a co-oxidant, molecular iodine works efficiently as an oxidant in catalytic quantity and it is environmentally benign compared to metal catalysts.[16] While a number of C−C bond-forming domino reactions are reported using iodine, there are only a few corresponding C−X (X = heteroatom) bond-forming processes.[17] Herein, we describe an efficient and metal-free synthesis of isatin and iodoisatin derivatives, starting from either 2′-NH_2 or 2′-*NH*-alkyl or 2′-*N,N*-dialkyl or 2′-*NH*-amidoacetophenones, using a I_2−TBHP−DMSO system.

RESULTS AND DISCUSSION

The study began with the reaction of compound **1a** with catalytic quantity of I_2 (0.05 equiv) and oxidant *t*-BuOOH

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Scheme 1. Strategies for Isatin Synthesis

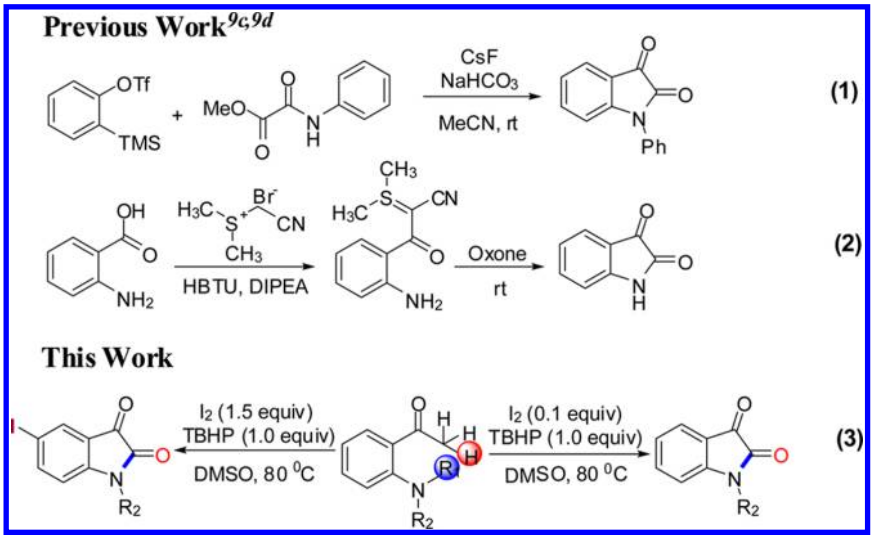
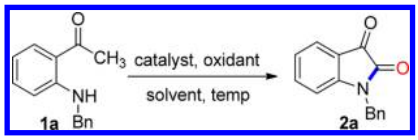


Table 1. Optimization Studies for the Synthesis of 1-Benzylindoline-2,3-dione[a]



entry	catalyst (equiv)	oxidant	solvent (equiv)	temp (°C)	time (h)	yield[b] (%)
1	I_2 (0.05)	TBHP (2.0)	DMSO	rt	24	nr
2	I_2 (0.05)	TBHP (2.0)	DMSO	80	13	58
3	I_2 (0.1)	TBHP (2.0)	DMSO	80	9	74
4	I_2 (0.1)	TBHP (1.0)	DMSO	80	7	86
5	I_2 (0.1)	TBHP (1.0)	DMSO	100	7	79
6	I_2 (0.1)	TBHP (1.0)	DMSO	60	12	74
7		TBHP (1.0)	DMSO	80	15	nd[c]
8	NIS (0.1)	TBHP (1.0)	DMSO	80	10	42
9	TBAI (0.1)	TBHP (1.0)	DMSO	80	12	47
10	KI (0.1)	TBHP (1.0)	DMSO	80	18	39
11	PIDA (0.1)	TBHP (1.0)	DMSO	80	20	trace
12	I_2 (0.1)	H_2O_2 (1.0)	DMSO	80	9	44
13	I_2 (0.1)	*m*-CPBA (1.0)	DMSO	80	9	36
14	I_2 (0.1)	Oxone (1.0)	DMSO	80	12	23
15	I_2 (0.1)		DMSO	80	14	21
16	I_2 (0.1)	TBHP (1.0)	DMF	80	12	n.d.[c]
17	I_2 (0.1)	TBHP (1.0)	toluene	80	12	trace
18	I_2 (0.1)	TBHP (1.0)	CH_3CN	80	12	n.d.[c]

[a]Reaction conditions: **1a** (1.0 mmol), catalyst (0.1 mmol), oxidant (1.0 mmol) in solvent (2.0 mL) at 80 °C. [b]Isolated yield. [c]Not determined.

(TBHP, 2.0 equiv) in DMSO. While there was no reaction at room temperature (rt, Table 1, entry 1), the desired product **2a** was obtained in 58% yield at 80 °C (entry 2). When the quantity of I_2 was increased to 0.1 equiv, the yield increased to 74% (entry 3). Interestingly, decreasing the quantity of TBHP to 1.0 equiv led to improved yield (86%, entry 4). Increasing or decreasing the temperature from 80 °C only led to a decrease in the yield (entries 5 and 6). In the absence of I_2, no compound **2a** was formed, which indicates that I_2 was crucial for the reaction (entry 7). Among the various iodine reagents such as NIS, TBAI, KI, and PIDA used for the study (entries 8−11), I_2 furnished compound **2a** in highest yield. Among various oxidants such as H_2O_2, *m*-CPBA, and Oxone, the best yield was observed with TBHP (entries 4 and 12−14), and the absence of oxidant (entry 15) led to lower yield. DMSO was the most effective medium for this oxidative cyclization compared to DMF, toluene, and CH_3CN. As a result, I_2 (0.1 equiv) and TBHP (1.0 equiv) in DMSO at 80 °C (Table 1, entry 4) were found to be the optimum conditions.

With the optimal reaction conditions in hand, the substrate scope was explored. As shown in Scheme 2, compound **1d** with primary amine afforded the isatin **2d** in moderate yield (42%). Compounds **1a−c** containing the *N*-benzyl class of substituent gave better yield compared to the *N*-alkyl-substituted counter parts **1e** and **1f**. Substrate **1g** with easily oxidizable *N*-allyl substituent gave isatin **2g** in 76% yield.

Similarly, compound **1h** with an *N*-phenyl substituent gave isatin **2h** in 74% yield. Likewise, *N*-(2-bromoethyl)-substituted 2′-aminoacetophenone **1j** formed isatin **2j** easily. Contrary to the failure met with the CuI/bpy system,[10e] compounds **1i**, **1s**, and **1t** underwent facile domino cyclization under the present reaction conditions. While compound **1i** with an *N*-ethyl acetate substituent gave isatin **2i** in 68% yield, compounds **1s** and **1t** underwent *N*-deacetylation (31%) and *N*-debenzoylation (28%), respectively, to provide isatin **2d** albeit in low yield. The presence of halogen, 4,6-$(OMe)_2$, and 2,3,4-$(OMe)_3$ substituents on the 2′-aminoacetophenone phenyl ring (**1k−r**) was well tolerated, and the corresponding products **2k−r** were obtained in 74%−85% yield.

Next, we examined the feasibility of isatin formation from tertiary aniline **3a−d** (Scheme 3). Surprisingly, tertiary aniline **3a** underwent demethylation followed by oxidative amidation to provide isatin **2u** in 76% yield. Under identical conditions, substrates **3b−d** were converted into corresponding isatins **2v**, **2w**, and **4d** in good yield (69%−78%). This result and earlier results (Scheme 2, **1d**, **1s**, and **1t**) shows that primary, secondary, tertiary aniline- and amido-substituted 2′-acetophenones can be converted into isatins by this oxidative amidation procedure.

The use of a stoichiometric amount of I_2 has a significant influence in the reaction. By varying the quantity of I_2, it was found that with 1.5 equiv of I_2 and 1.0 equiv of TBHP in

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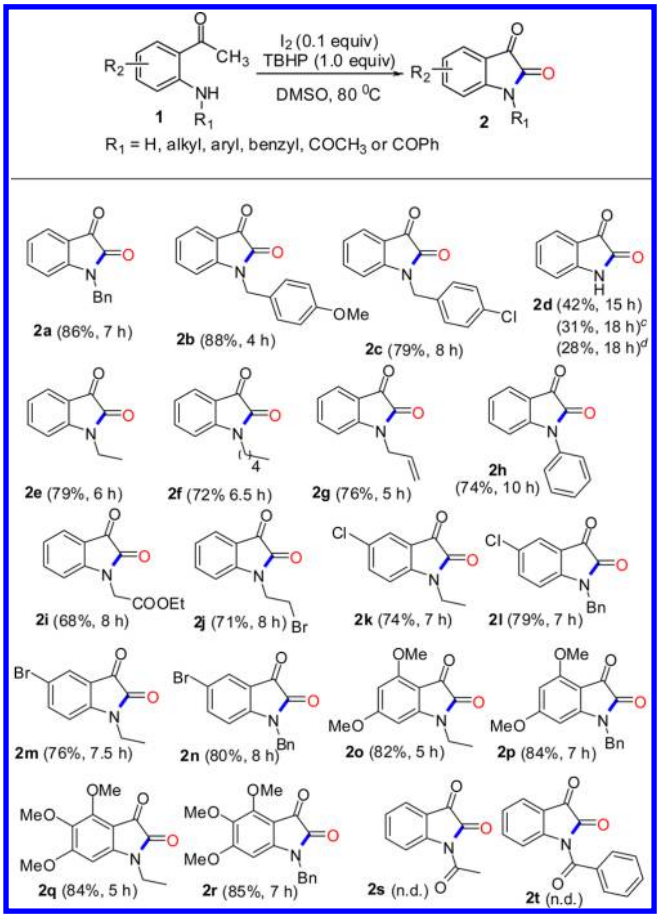
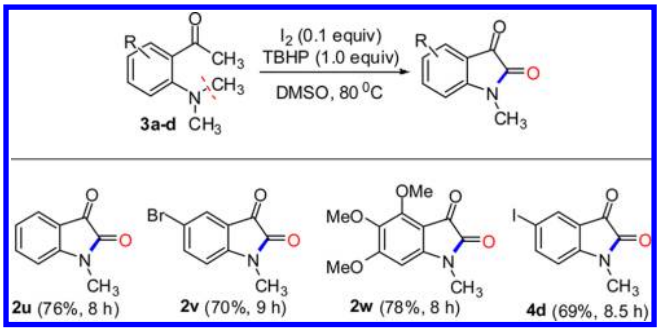
Scheme 2. Scope of Substitution Effect[a,b]



[a]Reaction conditions: **1a–q** (1.0 mmol), I_2 (0.1 mmol), TBHP (1.0 mmol) in DMSO (2 mL) at 80 °C. [b]Isolated yield. [c]**1s** used as starting material. [d]**1t** used as starting material.

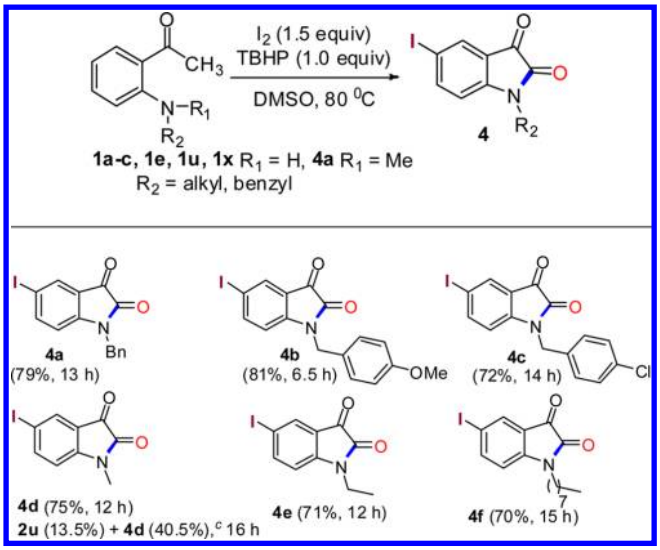
Scheme 3. I_2-Catalyzed Amidation of Tertiary Anilines[a,b]



[a]Reaction conditions: **3a–d** (1.0 mmol), I_2 (0.1 mmol), TBHP (1.0 mmol) in DMSO (2.0 mL) at 80 °C. [b]Isolated yield.

DMSO compound **1a** could be completely converted into iodoisatin **4a** (Scheme 4). When 1.0 equiv of I_2 and 1.0 equiv of TBHP in DMSO was used, a mixture of iodinated isatin **4a** and isatin **2a** was obtained. Under the same reaction conditions, the 2′-aminoacetophenones **1b,c,e,u,x** gave products **4b–f** in good yield (70%–81%). Under identical conditions, the tertiary aniline **4a** (Scheme 4) gave a 3:1 mixture of iodinated isatin **3d** (40.5%) and isatin **2u** (13.5%) after 16 h. This indicated that the oxidative amidation and iodination took place in one pot. To the best of our knowledge, this is the first example of the

Scheme 4. Synthesis of Substituted Iodoisatins Using a Stoichiometric Amount of I_2[a,b]

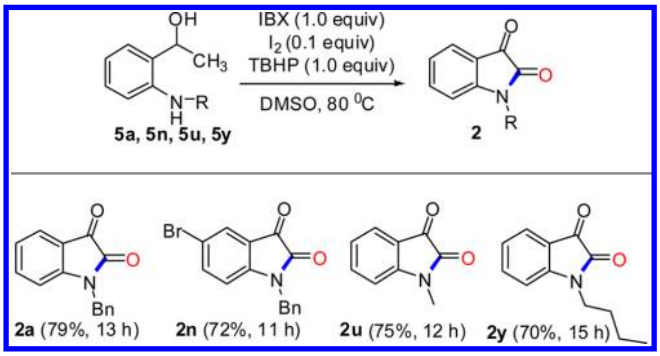


[a]Reaction conditions: **1** (1.0 mmol), I_2 (1.5 mmol), TBHP (1.0 mmol) in DMSO (2.0 mL) at 80 °C. [b]Isolated yield. [c]**4a** used as starting material.

synthesis of iodinated isatins, without a separate iodination step, via a domino process using molecular iodine as reagent as well as catalyst.

Next, the substrate scope was extended to benzyl alcohols (Scheme 5). On the basis of literature reports, we assumed that

Scheme 5. I_2-Catalyzed Amidation of Benzyl Alcohols[a,b]



[a]Reaction conditions: **5** (1.0 mmol), IBX (1.0 mmol), I_2 (0.1 mmol), TBHP (1.0 equiv) in DMSO (2.0 mL) at 80 °C. [b]Isolated yield.

alcohol **5a** in the presence of IBX could be easily oxidized to ketone,[18] which in turn would undergo amidation reaction with I_2/TBHP/DMSO to afford the corresponding isatins in one pot. Secondary alcohols **5a**, **5n**, **5u**, and **5y** underwent sequential oxidation followed by C–N bond formation to afford isatins **2a**, **2n**, **2u**, and **2y**, respectively, in high yield (70–79%).

To understand the reaction mechanism, some additional experiments were carried out (Scheme 6). Low yield (15%) or traces of isatin **2a** formation in the presence of aliphatic amine **6a** or **6b** (Scheme 6, eq 4) suggests *N*-I bond formation occurred by the more reactive aliphatic amine **6a** or **6b**, retarded Kornblum oxidation, or *N*-I bond formation by compound **1a**. Further, the formation of isatin **2d** from amides **1s** and **1t**, through *N*-deacetylation and *N*-debenzoylation,

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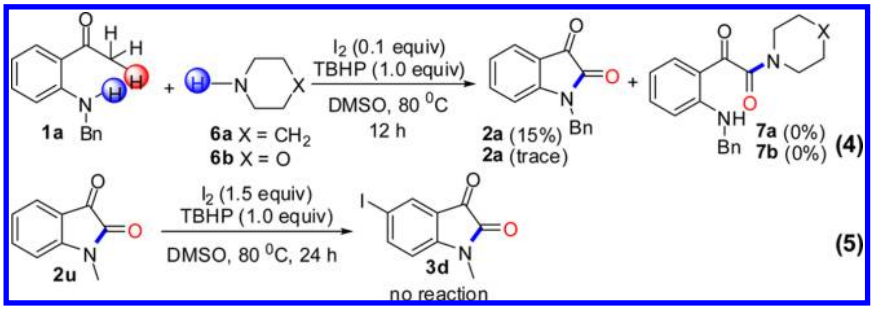
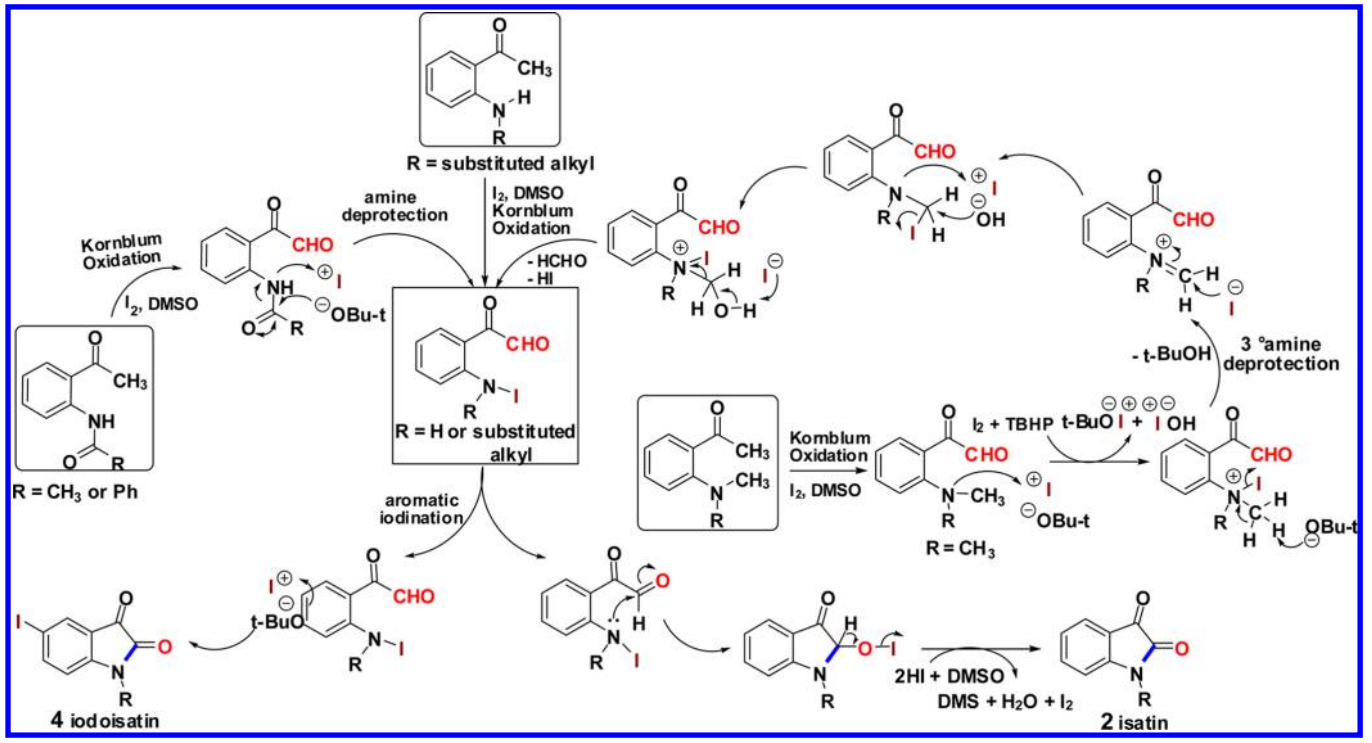
Scheme 6. Experiments To Study Mechanism



Scheme 7. Proposed Mechanism



respectively, supports the *N*-I bond formation (Scheme 2). Isatin **2u** did not undergo iodination (Scheme 6, eq 5), which reveals that the aromatic ring iodination should take place before the amidative ring closure.

On the basis of the above results, a plausible mechanism for the formation of isatin and iodoisatin is proposed (Scheme 7). The first step in isatin ring formation should be a facile Kornblum oxidation to form phenylglyoxal.[19] I^+ ions formed by the oxidation of I_2 in TBHP[20] may take part in iodination of amine as well as the aromatic ring and oxidative amidation steps. Subsequent intramolecular nucleophilic attack by the *N*-I bond to aldehyde is expected to lead to oxidative amidation. However, in case of primary, secondarym and tertiary anilines, it is difficult to rule out oxidative amidation taking place by intramolecular nucleophilic attack of an uniodinated amino group. The presence of DMSO helps regeneration of I_2 from HI. Secondary and tertiary anilines provide uniodinated isatins at lower concentration of I_2 (Scheme 2 and 3) and iodinated isatins at higher concentration of I_2 (Scheme 4), suggesting that Kornblum oxidation, *N*-iodination, and amido cyclization take place prior to aromatic iodination.

■ CONCLUSION

In conclusion, we have successfully developed a highly versatile, efficient, and metal-free synthesis of substituted isatins or iodoisatins, starting from 2′-*NH*$_2$, 2′-*NH*-alkyl, 2′-*N*,*N*-dialkyl, or 2′-*NH*-amidoacetophenones and 1-(2-aminophenyl)ethanols using I_2−TBHP as a catalyst. By varying the concentration of I_2, the reaction conditions can be fine-tuned to selective synthesis of isatin or iodoisatin. Overall, under the unimolecular approach, C−H, N−H, N−C bond cleavage as well as C−O, C−N, C−I bond formation was observed in one pot. A facile *N*-dealkylation and *N*-deacylation was observed for the first time in the presence of I_2−TBHP. We have also demonstrated that secondary alcohols could be oxidized in situ to give isatins. The reaction condition is mild and has broad substrate scope. Thus, this method is expected to be the simplest method for the synthesis of isatin or iodoisatin and find wide utility in organic synthesis. Studies on further scope of this reaction are underway in our laboratory.

■ EXPERIMENTAL SECTION

General Information. All reagents were purchased commercially and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on a 400 MHz spectrometer. ^{1}H NMR (400 MHz) and ^{13}C

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NMR (100 MHz) spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. All the NMR spectra were acquired at ambient temperature. 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. Elemental analysis was performed on a CHN analyzer.

General Method A: Typical Experimental Procedure for Synthesis of 1-(2-(Alkyl-/Arylamino)phenyl)ethanones. To a solution of 2′-aminoacetophenone (1.0 equiv) in DMF were added K_2CO_3 (1.5 equiv) and the corresponding halide (1.1 equiv) at ambient temperature and heated at 80 °C. Progress of the reaction was monitored by TLC. Upon completion of the reaction, it was allowed to cool to ambient temperature and diluted with ethyl acetate and water. 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, and the corresponding products were obtained in 70−75% yield.

General Method B: Typical Experimental Procedure for Synthesis of 1-(2-(Dimethylamino)phenyl)ethanones. To a solution of 2′-aminoacetophenone (1.0 equiv) in DMF were added K_2CO_3 (2.5 equiv) and methyl iodide (3.0 equiv) at ambient temperature and the solution heated at 80 °C for 8−10 h. Progress of the reaction was monitored by TLC. Upon completion of the reaction, it was allowed to cool to ambient temperature and diluted with ethyl acetate and water. 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, and the correcponding products were obtained in 78−82% yield.

General Method C: Typical Experimental Procedure for Synthesis of 1-(2-(Alkyl-/Benzylamino)phenyl)ethanol. To a solution of 2′-aminoacetophenone (1.0 equiv) in THF, sodium borohydride (1.5 equiv) was added at ambient temperature and stirred for 15 h. Upon completion of the reaction, it was diluted with ethyl acetate and water. 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, and the correcponding products were obtained in 72−75% yield.

General Method D: Typical Experimental Procedure for I_2-Catalyzed Synthesis of *N*-Alkyl-/Arylisatin. To a solution of 1-(2-(alkyl-/arylamino)phenyl)ethanone (**1**, 1.0 equiv) in DMSO were added I_2 (0.1 equiv) and TBHP (1.0 equiv, 70% in H_2O) at ambient temperature and the mixture heated at 80 °C. Progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was allowed to cool to ambient temperature and 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.

General Method E: Typical Experimental Procedure for I_2-Catalyzed Synthesis of 5-Iodo *N*-Alkyl-/Benzylisatin. To a solution of 1-(2-(alkyl-/benzylamino)phenyl)ethanone (**1**, 1.0 equiv) in DMSO were added I_2 (1.5 equiv) and TBHP (1.0 equiv, 70% in H_2O) at ambient temperature, and the mixture was heated at 80 °C. Progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was allowed to cool to ambient temperature and 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.

General Method F: Typical Experimental Procedure for I_2-Catalyzed Synthesis of *N*-Methylisatin from Tertiary Amines. To a solution of 1-(2-(dimethylamino)phenyl)ethanone (**4**, 1.0 equiv) in DMSO were added I_2 (0.1 equiv) and TBHP (1.0 equiv, 70% in H_2O) at ambient temperature, and the mixture was heated at 80 °C. Progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixturew was allowed to cool to ambient temperature and 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.

General Method G: Typical Experimental Procedure for I_2-Catalyzed Synthesis of *N*-Alkyl-/Benzylisatin from Secondary Alcohols. To a solution of 1-(2-(alkyl-/benzylamino)phenyl)ethanol (**5**, 1.0 equiv) in DMSO were added IBX (1.0 equiv), I_2 (0.1 equiv), and TBHP (1.0 equiv, 70% in H_2O) at ambient temperature, and the mixture was heated at 80 °C. Progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was allowed to cool to ambient temperature and 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.

1-Benzyl-1*H*-indole-2,3-dione (2a). The reaction was carried out according to general method D. Red solid: yield 86% (90.5 mg).

The reaction could also be carried out according to general method G. Red solid: yield 79% (82.4 mg); mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.2 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.37−7.29 (m, 5H), 7.09 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 158.29, 150.74, 138.35, 134.53, 129.07, 128.18, 127.45, 125.41, 123.88, 117.69, 111.03, 44.06. The spectral data of the compound **2a** was in agreement with the values reported in the literature.[21]

1-(4-Methoxybenzyl)-1*H*-indole-2,3-dione (2b). The reaction was carried out according to general method D. Red solid: yield 88% (92.1 mg); mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.2, 0.8 Hz, 1H), 7.48 (td, J = 7.9, 1.2 Hz, 1H), 7.28 (s, 2H), 7.08 (td, J = 7.6, 0.50 Hz, 1H), 6.87 (dd, J = 6.8, 2.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 4.86 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.37, 159.48, 158.24, 150.80, 138.23, 128.92, 126.50, 125.39, 123.78, 117.72, 114.43, 111.00, 55.30, 43.56. The spectral data of the compound **2b** was in agreement with the values reported in the literature.[22]

1-(4-Chlorobenzyl)-1*H*-indole-2,3-dione (2c). The reaction was carried out according to general method D. Red solid: yield 79% (82.6 mg); mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.6 Hz, 1H), 7.52−7.48 (m, 1H), 7.34−7.26 (m, 4H), 7.11 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 158.2, 150.4, 138.4, 134.14, 133.1, 129.3, 128.8, 125.6, 124.1, 117.7, 110.8, 43.4. The spectral data of the compound **2c** was in agreement with the values reported in the literature.[23]

1*H*-Indole-2,3-dione (2d). The reaction was carried out according to general method D. Red solid: yield 42% (45.7 mg).

The reaction was also carried out according to general method D. Red solid: yield 31% (25.7 mg).

The reaction was also carried out according to general method D. Red solid: yield 28% (17.2 mg). The compound **2d** is commercially available.

1-Ethyl-1*H*-indole-2,3-dione (2e). The reaction was carried out according to general method D. Red solid: yield 79% (84.8 mg); mp 87−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.56 (m, 2H), 7.11 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 3.78 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 157.0, 149.7, 137.3, 124.5, 122.6, 116.6, 109.0, 34.0, 11.5. The spectral data of the compound **2e** were in agreement with the values reported in the literature.[21]

1-Pentyl-1*H*-indole-2,3-dione (2f). The reaction was carried out according to general method D. Semisolid: yield 72% (76.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.57 (m, 2H), 7.11 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 3.71 (t, J = 7.2 Hz, 2H), 1.72−1.68 (m, 2H), 1.38−1.34 (m, 4H), 0.90 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 158.2, 151.1, 138.3, 125.4, 123.6, 117.6, 110.2, 40.3, 29.0, 27.0, 22.3, 14.0 The spectral data of the compound **2f** were in agreement with the values reported in the literature.[24]

1-Allyl-1*H*-indole-2,3-dione (2g). The reaction was carried out according to general method D. Red solid: yield 76% (81.2 mg); 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,

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$CDCl_3$) δ 183.3, 158.0, 151.0, 138.3, 130.35, 125.4, 124.9, 118.7, 117.6, 111.0, 42.5. The spectral data of the compound **2g** were in agreement with the values reported in the literature.[25]

1-Phenyl-1*H*-indole-2,3-dione (2h). The reaction was carried out according to general method D. Red solid: yield 74% (78.1 mg); mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.6, 0.6 Hz, 1H), 7.58−7.51 (m, 3H), 7.47−7.41 (m, 3H), 7.19−7.15 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 157.3, 151.8, 138.3, 133.0, 130.0, 128.9, 126.04, 125.6, 124.3, 117.6, 111.3. The spectral data of the compound **2h** were in agreement with the values reported in the literature.[10e]

Ethyl 2-(2,3-Dioxoindolin-1-yl)acetate (2i). The reaction was carried out according to general method D. Red solid: yield 68% (71.6 mg); mp 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.57 (m, 2H), 7.16 (t, m = 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, 138.41, 125.6, 124.2, 117.7, 110.1, 62.2, 41.3, 14.1. The spectral data of the compound **2i** were in agreement with the values reported in the literature.[21]

1-(2-Bromoethyl)indoline-2,3-dione (2j). The reaction was carried out according to general method D. Red solid: yield 71% (74.5 mg); mp 131−133 °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 182.7, 158.2, 150.5, 138.4, 125.8, 124.1, 117.7, 110.2, 42.0, 27.1. The spectral data of the compound **2j** were in agreement with the values reported in the literature.[21]

5-Chloro-1-methyl-1*H*-indole-2,3-dione (2k). The reaction was carried out according to general method D. Red solid: yield 74% (78.8 mg); mp 157−159 °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. The spectral data of the compound **2k** were in agreement with the values reported in the literature. [26]

5-Bromo-1-benzyl-1*H*-indole-2,3-dione (2l). The reaction was carried out according to general method D. Red solid: yield 79% (82.6 mg); mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.0 Hz, 1H), 7.37−7.35 (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, 157.8, 149.0, 137.7, 134.0, 129.8, 129.2, 128.4, 127.4, 125.4, 118.5, 112.3, 44.2. The spectral data of the compound **2l** were in agreement with the values reported in the literature.[27]

5-Bromo-1-ethyl-1*H*-indole-2,3-dione (2m). The reaction was carried out according to general method D. Red solid: yield 76% (79.7 mg); mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 2 Hz, 2H), 7.70 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 3.78 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 157.2, 149.4, 140.5, 128.3, 118.8, 116.4, 111.7, 35.1, 12.4. The spectral data of the compound **2m** were in agreement with the values reported in the literature.[28]

5-Bromo-1-benzyl-1*H*-indole-2,3-dione (2n). The reaction was carried out according to general method D. Red solid: yield 80% (83.1 mg).

The reaction was also carried out according to general method G: yield 72% (74.3 mg); mp 149−150 °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 182.1, 157.5, 149.4, 140.5, 134.0, 129.2, 128.4, 128.2, 127.4, 118.9, 116.8, 112.7, 44.2. The spectral data of the compound **2n** was in agreement with the values reported in the literature.[27]

1-Ethyl-4,6-dimethoxy-1*H*-indole-2,3-dione (2o). The reaction was carried out according to general method D. Yellow solid: yield 82% (86.3 mg); mp143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.71 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 170.1, 161.3, 159.8, 153.3, 100.7, 91.6, 90.5, 56.3, 56.2, 35.0, 13.0. The spectral data of the compound **2o** were in agreement with the values reported in the literature.[10f]

1-Benzyl-4,6-dimethoxy-1*H*-indole-2,3-dione (2p). The reaction was carried out according to general method D. Yellow solid; yield 84% (87.5 mg); mp181−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.98 (d, J = 2.0 Hz, 1H), 5.89 (d, J = 2.0 Hz, 1H), 4.86 (s, 2H), 3.94 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 170.0, 161.2, 160.2, 153.3, 135.1, 129.0, 128.0, 127.3, 100.9, 91.9, 91.5, 56.3, 56.1, 44.0. The spectral data of the compound **2p** was in agreement with the values reported in the literature.[10f]

1-Ethyl-4,5,6-trimethoxy-1*H*-indole-2,3-dione (2q). The reaction was carried out according to general method D. Red solid: yield 84% (87.9 mg); mp 115−117 °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), 3.74 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 162.4, 159.0, 154.3, 148.7, 136.3, 102.5, 89.4, 62.2, 61.5, 56.9, 34.8, 13.0. The spectral data of the compound **2q** was in agreement with the values reported in the literature.[10f]

1-Benzyl-4,5,6-trimethoxy-1H-indole-2,3-dione (2r). The reaction was carried out according to general method D. Red solid: yield 85% (88.2 mg); mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.99 (s, 1H), 4.89 (s, 2H), 4.20 (s, 3H), 3.81 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 162.2, 159.4, 154.2, 148.7, 136.4, 135.0, 129.1, 128.2, 127.3, 102.6, 90.5, 62.3, 61.5, 56.6, 44.0. The spectral data of the compound **2r** were in agreement with the values reported in the literature. [10f]

1-Methyl-1*H*-indole-2,3-dione (2u). The reaction was carried out according to general method F. Red solid: yield 76% (75.0 mg).

The reaction was carried out according to general method G: yield 75% (79.9 mg); mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.59 (m, 2H), 7.13 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 158.3, 151.5, 138.4, 125.3, 123.9, 117.5, 109.9, 26.2. The spectral data of the compound **2u** were in agreement with the values reported in the literature.[21]

5-Bromo-1-methyl-1*H*-indole-2,3-dione (2v). The reaction was carried out according to general method F. Red solid: yield 70% (69.4 mg); mp 173−175 °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, 150.2, 140.6, 128.1, 118.6, 116.7, 111.6, 26.4. The spectral data of the compound **2v** was in agreement with the values reported in the literature.[26]

1-Methyl-4,5,6-trimethoxy-1*H*-indole-2,3-dione (2w). The reaction was carried out according to general method F. Red solid: yield 78% (77.3 mg); mp 110−112 °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), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 161.3, 158.3, 153.3, 148.5, 135.5, 101.3, 88.3, 61.3, 60.5, 55.8, 28.7, 25.2. The spectral data of the compound **2w** were in agreement with the values reported in the literature.[10f]

1-Butyl-1*H*-indole-2,3-dione (2x). The reaction was carried out according to general method G. Semisolid: yield 70% (74.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.56 (m, 2H), 7.13−7.09 (m, 1H), 6.90 (d, J = 7.6 Hz, 1H), 3.72 (t, J = 7.2 Hz, 2H), 1.72−1.62 (m, 2H), 1.46−1.37 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 158.2, 151.1, 138.3, 125.5, 123.6, 117.6, 110.2, 40.0, 29.30, 20.2, 13.7. The spectral data of the compound **2x** were in agreement with the values reported in the literature.[21]

5-Iodo-1-benzyl-1*H*-indole-2,3-dione (4a). The reaction was carried out according to general method E. Red solid: yield 79% (127.3 mg); mp 151−153 °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, 157.3, 150.0, 146.3, 134.0, 133.9, 129.2, 128.4, 127.4, 119.2, 113.1, 86.2, 44.2. The spectral data of the compound **4a** were in agreement with the values reported in the literature.[29]

5-Iodo-1(4-methoxybenzyl)-1*H*-indole-2,3-dione (4b). The reaction was carried out according to general method E. Red solid: yield 81% (124.7 mg); mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.76 (dd, J = 8.4, 1.6 Hz, 1H), 7.26−7.22 (m, 2H), 6.86 (dd, J = 6.8, 2.0 Hz, 2H), 6.59 (d, J = 8.4 Hz, 1H), 4.84 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.0, 159.6, 157.2, 150.1, 146.3, 133.8, 128.9, 126.0, 119.3, 114.5, 113.2, 86.1, 55.3, 43.7. The

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spectral data of the compound **4b** were in agreement with the values reported in the literature.[30]

1-(4-Chlorobenzyl)-5-iodo-1*H*-indole-2,3-dione (4c). The reaction was carried out according to general method E. Red solid: yield 72% (110.2 mg); mp 206−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.79 (dd, J = 8.2, 1.8 Hz, 1H), 7.34−7.31 (m, 2H), 7.26 (d, J = 2.0 Hz, 1H), 7.23 (s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 4.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 157.2, 149.7, 146.4, 134.4, 134.0, 132.6, 129.4, 128.8, 119.3, 112.9, 86.4, 43.5; MS (ESI): 397.11 (M + 1) for $C_{15}H_9ClINO_2$. Anal. Calcd for $C_{15}H_9ClNO_2$: C, 45.31; H, 2.28. Found: C, 45.28; H, 2.31.

5-Iodo-1-methyl-1*H*-indole-2,3-dione (4d). The reaction was carried out according to general method E. Red solid: yield 75% (144.3 mg).

The reaction was also carried out according to general method E: yield 54% (94.9 mg).

The reaction was also carried out according to general method F: yield 69% (68.5 mg); mp 161−163 °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 182.0, 157.2, 150.8, 146.4, 133.8, 119.0, 112.1, 86.0, 26.3. The spectral data of the compound **4d** was in agreement with the values reported in the literature. [29]

5-Iodo-1-ethyl-1*H*-indole-2,3-dione (4e). The reaction was carried out according to general method E. Red solid: yield 71% (130.9 mg); mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 182.3, 156.9, 150.0, 146.3, 134.0, 119.2, 112.1, 85.8, 35.1, 12.4. The spectral data of the compound **4e** was in agreement with the values reported in the literature. [29]

5-Iodo-1-octyl-1*H*-indole-2,3-dione (4f). The reaction was carried out according to general method E. Red solid: yield 70% (109 mg); mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.79 (m, 2H), 6.64 (d, J = 8.8 Hz, 1H), 3.62 (t, J = 7.4 Hz, 2H), 1.63−1.56 (m, 2H), 1.27−1.18 (m, 11H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 156.1, 149.4, 145.3, 132.9, 118.1, 111.3, 84.8, 39.4, 30.7, 28.1, 28.1, 26.2, 25.9, 21.6, 13.0; MS (ESI) 386.31 (M + 1) for $C_{16}H_{20}INO_2$. Anal. Calcd for $C_{16}H_{20}INO_2$: C, 49.88; H, 5.23. Found: C, 49.67; H, 5.28.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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