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Generation of Aryl Radicals from Aryl Hydrazines via Catalytic Iodine in Air: Arylation of Substituted 1,4-Naphthoquinones

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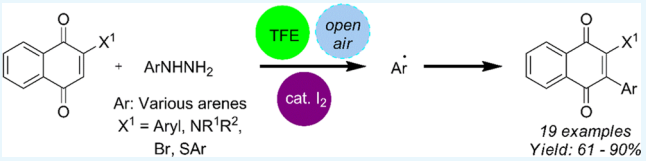
ABSTRACT: Arylated building blocks or heterocycles are key to myriad applications, including pharmaceutical drug discovery, materials sciences, and many more. Herein, we have reported a mild and efficient strategy for generation of aryl radicals by reacting appropriate aryl hydrazines with catalytic iodine in open air. The aryl radicals were quenched by diversely substituted 1,4-napthoquinones present in the reaction mixture to afford diversely substituted 2,3-napthoquinones in moderate to excellent yield. Control experiments provided insights into the putative reaction mechanism.



INTRODUCTION

Aryl radicals are highly reactive intermediates that play a crucial role in diverse organic transformations, such as halogen-transfer biaryl couplings, Sandmeyer reactions, addition to iminium ions, addition to sulfur dioxide, and reactions with electron-deficient alkenes (Meerwein's arylation) and alkynes.[1a−k] Due to their versatile utility, there have been quite a few synthetic strategies to generate them. Among the most popular ones are through diazonium salts and reactions of aryl bromides or iodides with tributyl tin hydride and similar silicon hydrides.[2a−c] They can also be accessed through electrochemical reactions of aryl halides and aryl hydrazines.[3] Recently, Liu and co-workers generated *N*,*N*′-diacylhydrazine from (bis(trifluoroacetoxy)-iodo)benzene (PIFA) and *N*-acetylphenylhydrazide at a mild temperature.[4] The phenyl radical (generated from the *N*-acetyl-*N*′-phenylhydrazide under oxygen in PIFA) plays a crucial role in the transformation.[4] Aryl radicals are also generated by treating aryl hydrazines or aryl hydrazine hydrochlorides with bases (such as pyridine, sodium hydroxide, and potassium carbonate) in the presence of air.[5a−c] These aryl radicals are eventually quenched by various heteroaromatic or heterocycle building blocks, such as pyrrolidine, pyridine, chromones, etc., to provide the corresponding arylated species.[5a−c]

By virtue of their ubiquitous presence in nature and their role as inhibitors in diverse biological systems, such as bacteria, fungi, mammals, and parasites, naphthoquinones hold a niche position in synthetic and medicinal chemistry.[6a−k] They have displayed diverse activities as antibiotic, antifungal, anti-inflammatory, anti-allergic, apoptotic, and antithrombotic agents.[6a−e] Aryl naphthoquinones form an exclusive class of natural products and are found as building blocks in crisamicin A, microphyllaquinone, conocurvone, etc.[6f−k]

Despite their vast application as curative agents there are not very many efficient synthesis protocols of arylated naphthoquinones (Scheme 1). A few general strategies include metal-mediated oxidation and cycloaddition of aromatics (Scheme 1a), base-mediated arylation of naphthoquinones with aryldiazonium salts (Scheme 1b), and C−H bond activation via transition-metal-catalyzed coupling reactions (Scheme 1c), and there have been a few recent reports on hypervalent iodine as a reagent in this transformation (Scheme 1d).[7−10] Among these strategies, the transition-metal-catalyzed pathway has been harnessed to a greater extent. For example, palladium-catalyzed coupling of substituted 1,4-naphthoquinones with arenes (e.g., organostannanes, halides, or boronic acids) afforded the desired 2- or 3-aryl naphthoquinones in decent yield.[9a−h] A close scrutiny of these strategies reveals myriad disadvantages associated with them. For example, the strategies applied to date have only provided a limited number of analogues (4−6) and are extremely substrate-specific (Scheme 1a−d). The majority of these reactions involved harsh conditions such as high temperature and application of toxic metals, such as chromium, as reagents or heavy metal palladium catalysts (Scheme 1b). Other than the transition-metal-catalyzed procedures, the remaining strategies used a stoichiometric amount of reagents (Scheme 1a,b and d) for the arylation of 1,4-naphthoquinones. Hence, development of a metal-free, environmentally benign catalytic strategy will be of tremendous advantage.

Iodine and organic iodides have evolved as efficient and robust reagents or catalysts for the synthesis of organic compounds.[11,12] One of the most remarkable developments in this field is the invention of the catalytic activity of molecular iodine in the formation of diverse C−C, C−O, and C−N bonds.[13a−c] Interestingly, iodine- and transition-metal-catalyzed reactions are similar and the fact that iodine is environmentally

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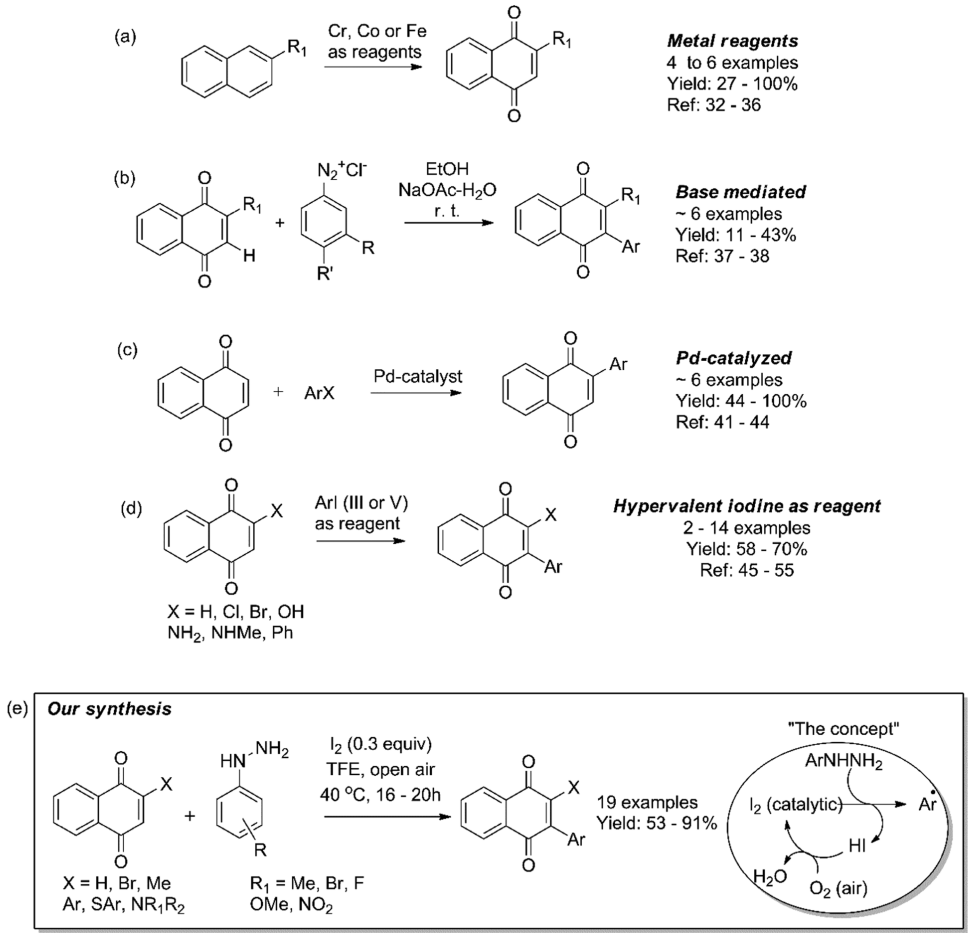
Scheme 1. Existing Strategies and Our Methodology



benign, robust, and inexpensive provides an enormous scope for these reactions in industry if properly harnessed.[14]

As a sustainable and viable contribution toward the generation of aryl radicals, we began to think about harnessing molecular iodine as an appropriate catalyst. From the literature survey, we realized that in the presence of air, hydroiodic acid is oxidized to molecular iodine. There is also a report by Joshi and co-workers published in 1957 that described the generation of aryl radicals by the treatment of dinitrophenyl hydrazine with a stoichiometric quantity of iodine.[15a,b] On the basis of these studies, we envisioned a reaction of 1,4-naphthaquinone with phenyl hydrazine in air with catalytic molecular iodine. We anticipated that the hydroiodic acid generated in the reaction will be oxidized back to molecular iodine, thereby creating a catalytic cycle (Scheme 1j, "The concept"). In that direction, herein, we demonstrate the generation of aryl radicals from catalytic iodine in an open air vessel, with trifluoroethanol (TFE) as a solvent at 40 °C. For the first time, molecular iodine has been leveraged as a catalyst for this reaction. The aryl radicals were subsequently quenched with substituted 1,4-naphthoquinones to provide a diverse library of arylated 1,4-naphthoquinones in moderate to excellent yield (Scheme 1j).

RESULTS AND DISCUSSION

Optimization of Radical Generation and Subsequent Quenching with Substituted 1,4-Naphthoquinone. We began our optimization studies with 2-(4-thioanisolyl)-1,4-naphthoquinone **1a** and 4-methoxyphenyl hydrazine **2a** as the model reaction partners (Table 1). Various solvents were explored with a variety of iodine-based compounds as reagents or catalysts (Table 1, entries 1−21). The reaction temperature ranged from room temperature (r.t.) to 70 °C. The first reaction with a stoichiometric amount of phenyl iodonium diacetate (PIDA, 1 equiv) under a nitrogen atmosphere at r.t. in acetonitrile (ACN) afforded the desired compound **3a** in 44% yield (Table 1, entry 1). A reaction with (bis(trifluoroacetoxy)-iodo)benzene (PIFA) (1 equiv) afforded **3a** in a similar yield of 42% (Table, entry 2). The same reactions with PIDA and PIFA in the presence of oxygen provided **3a** in slightly better yield (Table 1, entries 3 and 4). Reactions with 1 equiv of tetrabutylammonium iodide (TBAI) (in ACN/H_2O = 1:3 solvent system) and molecular iodine (I_2) (with ACN as solvent) drastically improved the yield to ∼75% (Table 1, entries 5 and 6). All of these aforementioned reactions occurred at r.t. To evaluate the catalytic scope of TBAI, next it was used in 0.1 equiv in the presence of 0.2 equiv of pyridine in 1:3 ACN/H_2O under an oxygen atmosphere at r.t. and at 70 °C (Table 1, entries 7 and 8). The reaction at 70 °C yields nearly 80% of **3a** (Table 1, entry 8). The reactions with only 0.5 equiv of TBAI (Table 1, entry 9) or with 0.5 equiv of pyridine (Table 1, entry 10) provided 18−21% of **3a**. This emphasizes the combined importance of both TBAI and pyridine in the reaction. It was interesting to explore the effect of catalytic molecular iodine on the reaction. Accordingly, reactions were conducted with 0.3 equiv of molecular iodine in ACN at 40 °C in the presence of 0.3 equiv of pyridine (Table 1, entry 11) and 1 equiv of hydrogen

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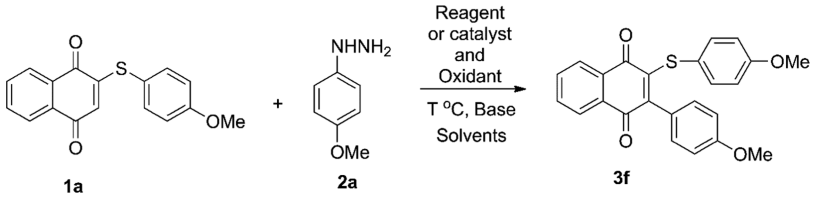
Table 1. Optimization of the Reaction Conditions for Generation of Aryl-1,4-naphthoquinone[c]



entry	reagent/catalyst (equiv)	N_2/O_2/air	solvent	time (h)	temperature (°C)	yield (%)[b]
1	PIDA (1)	N_2	CH_3CN	16	r.t.	44
2	PIFA (1)	N_2	CH_3CN	16	r.t.	42
3	PIDA (1)	O_2	CH_3CN	16	r.t.	45
4	PIFA (1)	O_2	CH_3CN	16	r.t.	49
5	TBAI (1)	O_2	CH_3CN	15	r.t.	75
6	I_2 (1)	O_2	CH_3CN	16	r.t.	74
7[a]	TBAI (0.1)	O_2	CH_3CN/H_2O (1:3)	18	r.t.	22
8	TBAI (0.1)	O_2	CH_3CN/H_2O (1:3)	16	70	80
9	TBAI (0.5)	O_2	CH_3CN/H_2O (1:3)	16	70	21
10	pyridine (0.5)	O_2	CH_3CN/H_2O (1:3)	16	70	18
11	I_2 (0.3)/pyridine (0.3)	air	CH_3CN	17	40	81
12	I_2 (0.3)/H_2O_2 (1)	air	CH_3CN	19	40	78
13	I_2 (0.3)	air	CH_3CN	19	40	77
14	I_2 (0.3)	air	CH_3CN/H_2O (1:3)	19	40	18
15	I_2 (0.3)	air	MeOH	14	40	56
16	I_2 (0.3)	air	TFE	17	40	91
17	I_2 (0.3)	air	IPA	18	40	21
18	I_2 (0.3)	air	HFIP	20	40	43
19	I_2 (0.3)	air	DCM	17	40	12
20	I_2 (0.1)	air	TFE	39	40	81
21	I_2 (0.2)	air	TFE	41	40	86

[a]With 0.2 equiv of pyridine. [b]Isolated yield. [c]Exploratory reactions took place with 1 equiv of **1a** (in 50 mg scale) and 2 equiv of **2a**.

peroxide (H_2O_2) (Table 1, entry 12) to afford **3a** in nearly similar yield to that in entry 8. The average reaction time for all of these reactions ranged between 16 and 20 h. To seek an environmentally more conducive reaction condition, the molecular-iodine-catalyzed reactions were next conducted under base-free conditions in open air in various solvents (Table 1, entries 13−19). To our utmost satisfaction, among these reactions, the reaction in 2,2,2-trifluorethanol (TFE) provided **3a** in the best yield of 91% (Table 1, entry 16). This result is extremely significant as, in sustainable chemistry, TFE is an archetypal solvent due to its strong ability for hydrogen-bond donation, high ionizing ability, and environmentally friendly characteristics. It is noteworthy that the reaction in methanol was more rapid than that in TFE (12 vs 16 h); however, it generated the biphenyl byproduct in substantial quantities that rendered it less efficient (Table 1, entry 15). Reducing the equivalents of iodine to 0.1 and 0.2 equiv slowed the reactions (Table 1, entries 20 and 21). They took nearly 40 h to complete. Hence, the optimized protocol involved the reaction of 0.3 equiv of iodine, 1 equiv of **1a**, and **2a** in the presence of TFE under open air at 40 °C to afford the desired arylated 1,4-naphthoquinone **3a** as the desired product (Table 1).

Exploring the Generic Nature of the Reaction. With the optimized conditions in hand, various 2- or 3-aryl-substituted 1,4-naphthoquinones were generated that proved the robust nature of the protocol. In general, a variety of substituted 1,4-naphthoquinones were chosen as substrates. It is noteworthy that a few of the analogues synthesized via our strategy are known, but most of them are new and the choice of analogues highlights the simplicity and diversity of our strategy. The amino- and thio-substituted naphthoquinone substrates, such as 2-(4-thioanisolyl) **1a**, 2-thiophenyl **1b**, 2-(4-fluorothiophenyl) **1c**, 2-piperidinyl **1d**, and 2-*N*-methyl-*N*-benzylamino **1e**, were purposefully chosen to demonstrate the robustness of our protocol amid the heteroaryl functionalities. In addition, 2-bromo- and 2-methyl-substituted 1,4-naphthoquinones **1f** and **1g**, respectively, were also subjected to the optimized reaction conditions with a variety of aryl hydrazines, viz., 4-anisolyl hydrazine, phenyl hydrazine, and 3-fluorophenyl hydrazine **2a**−**c**, to generate the desired products **3a**−**n** in moderate to excellent yield (Scheme 2). In general, the thioaryl-substituted 1,4-naphthoquinones, such as **1a**−**c**, were the most amenable toward our optimized conditions. The corresponding desired products **3a**−**g** were obtained in 84−90% yield (Scheme 2). The next best substrates were the amino-substituted naphthoquinones **1d** and **1e**. Accordingly, products **3h**−**k** were obtained in 66−75% yield. The 2-bromo- and 2-methyl-substituted analogues **1f**,**g** afforded the desired products **3l**−**n** in 55−63% yield, respectively (Scheme 2).

Next, the unsubstituted 1,4-naphthoquinone **1h** was subjected to the same reaction conditions with 4-anisolyl hydrazine, phenyl hydrazine, and 2,4-dinitrophenyl hydrazine, **2a**,**b**, and **d** (Scheme 3). The reaction afforded the desired mono- and disubstituted products **3o**−**s** in moderate yields of 23−82%. **2a** and **2d** provided the monoarylated products **3p** and **3o**, respectively, whereas **2b** generated both the mono- and diarylated compounds **3q** and **3r**, respectively, with **3r** being the major product (Scheme 2). **3p**, when reacted under optimized conditions with phenyl hydrazine **2b**, afforded the

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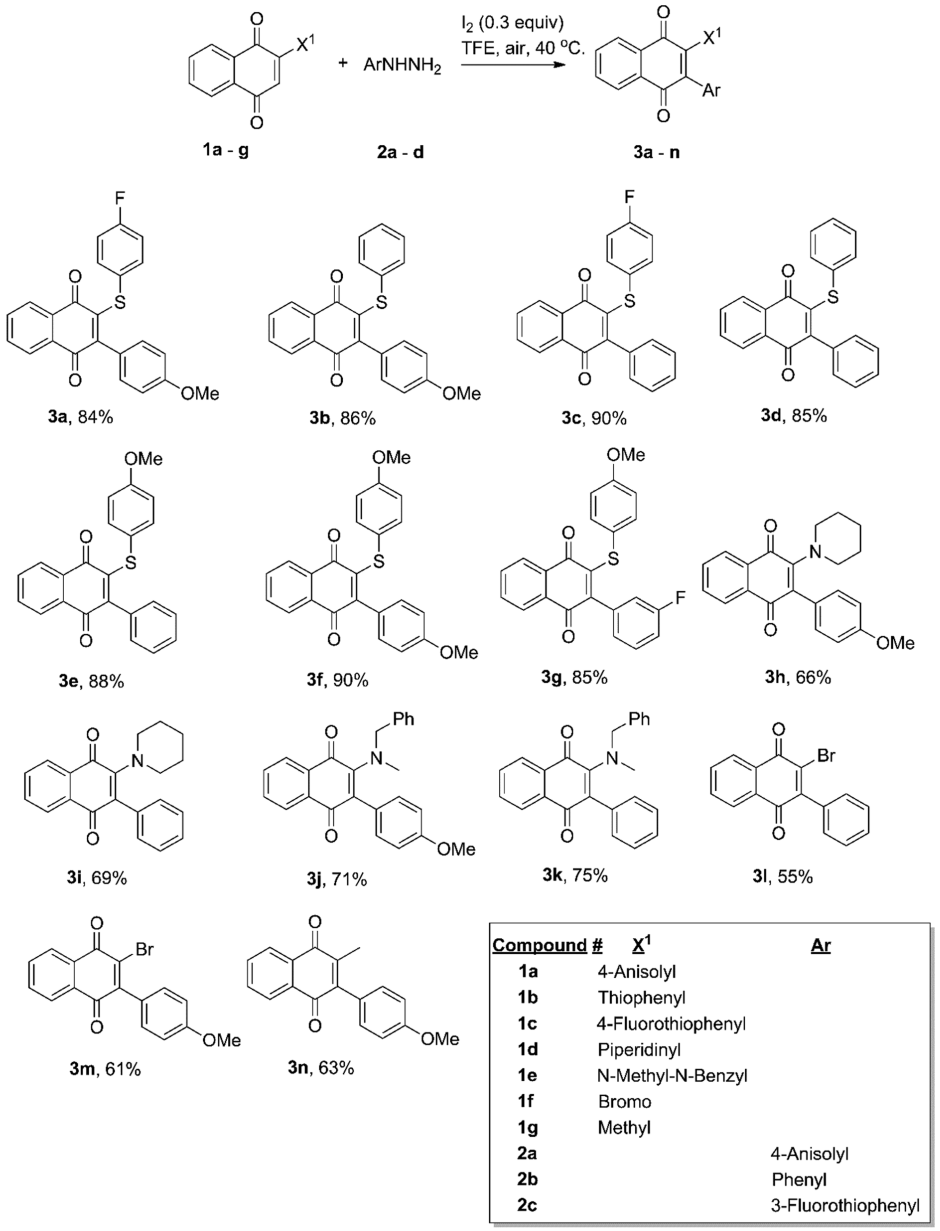
Scheme 2. Library of Arylated Naphthoquinones



diarylated naphthoquinone derivative **3s** in excellent yield (Scheme 3).

Control Experiments. To understand the mechanism of the reaction, a few control experiments were conducted. When **1a** was reacted with 0.3 equiv of molecular iodine in TFE at 40 °C under air in the absence of phenyl hydrazine, it did not generate 2-iodo-3-thioanisole-1,4-naphthoquinone **3a′**, thereby indicating that no iodination of substrate **1a** occurred in the presence of molecular iodine (Scheme 4a) and that molecular iodine specifically reacted with aryl hydrazine to generate the aryl radicals. Next, the reaction in deuterated methanol (CD_3OD) provided the desired product **3a** along with the formation of deuterated-[D_1]-**1a** and unreacted starting material **1a**, thereby indicating the radical-mediated reversible C−H bond formation at the quinonoid moiety of substrate **1a** during the reaction (Scheme 4b) (see Scheme S1 and Figure S1 in the Supporting Information). However, stirring substrate **1a** in CD_3OD for 6 h did not provide the scrambled substrate. When 1.5 equiv of (α-(4-pyridyl-1-oxide)-*N*-*tert*-butyl nitrone (POBN), a spin-trap reagent that traps organic radicals) was reacted with **2b** in the presence of 0.3 equiv of molecular iodine under air at 40 °C in TFE, the desired phenyl-POBN adduct **4** was detected as the major product in the mass spectra (Scheme 4c) (see Scheme/Figure S2 in the Supporting Information). This substantiated the generation of aryl radicals in the presence of catalytic molecular iodine. To understand the contribution of air, **1a** and **2b** were reacted under optimized reaction conditions, which resulted in the formation of **3a** in 16% yield. Hence, air is required to sustain the catalytic cycle (Scheme 4d). Finally, when **1a** was reacted with phenyl diazonium tetrafluoroborate (Scheme 4e) in the presence of iodine, the desired product **3a** was obtained as indicated in the mass spectra (Scheme 4e) (see Scheme S3 and the related procedure in the Supporting Information).

Reaction Mechanism. Based on the control experiments, the mechanism of arylation of substituted 1,4-naphthoquinone

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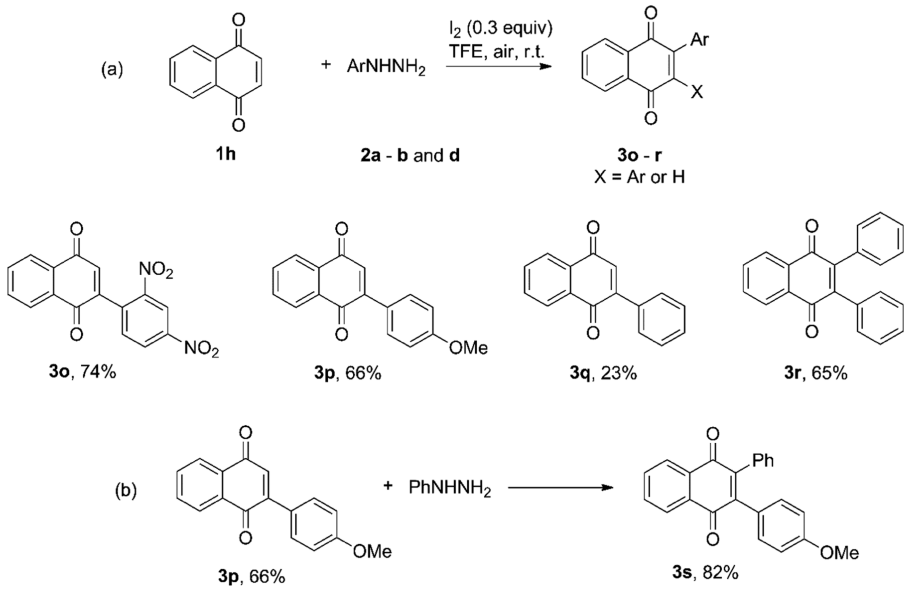
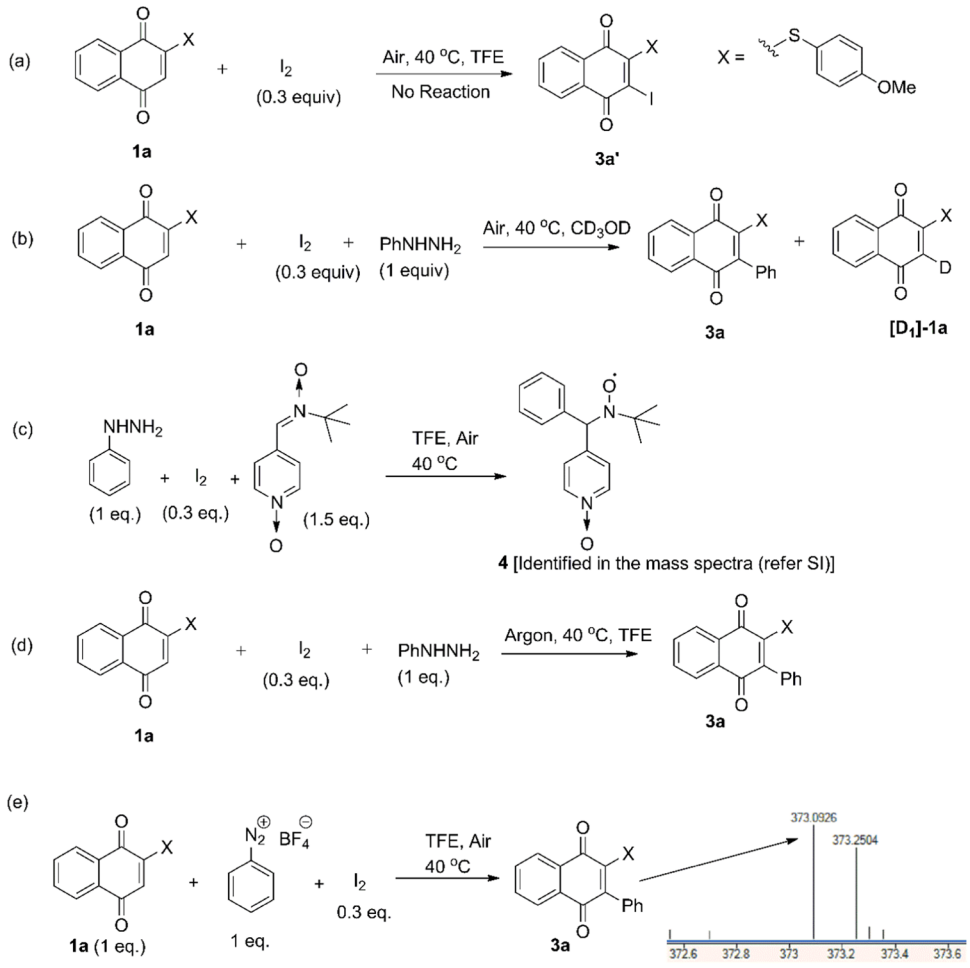
Scheme 3. Arylation of Unsubstituted 1,4-Naphthoquinone



Scheme 4. Control Experiments to Understand the Molecular-Iodine-Catalyzed Generation of an Aryl Radical in Air and Its Subsequent Quenching with Substituted 1,4-Naphthoquinone



is proposed in Scheme 5. Initially, iodine reacts with phenyl hydrazine **2b** to afford intermediate **A**. Dehydroiodination of **A** leads to the formation of **B**, which further reacts with molecular iodine (regenerated from the air oxidation of hydroiodic acid obtained during the formation of **B**) to provide **C**. During the entire process, the hydroiodic acid formed is converted to molecular iodine via air oxidation, thereby the catalytic cycle of the reaction is sustained.[15] Charge transfer of **C** provided the

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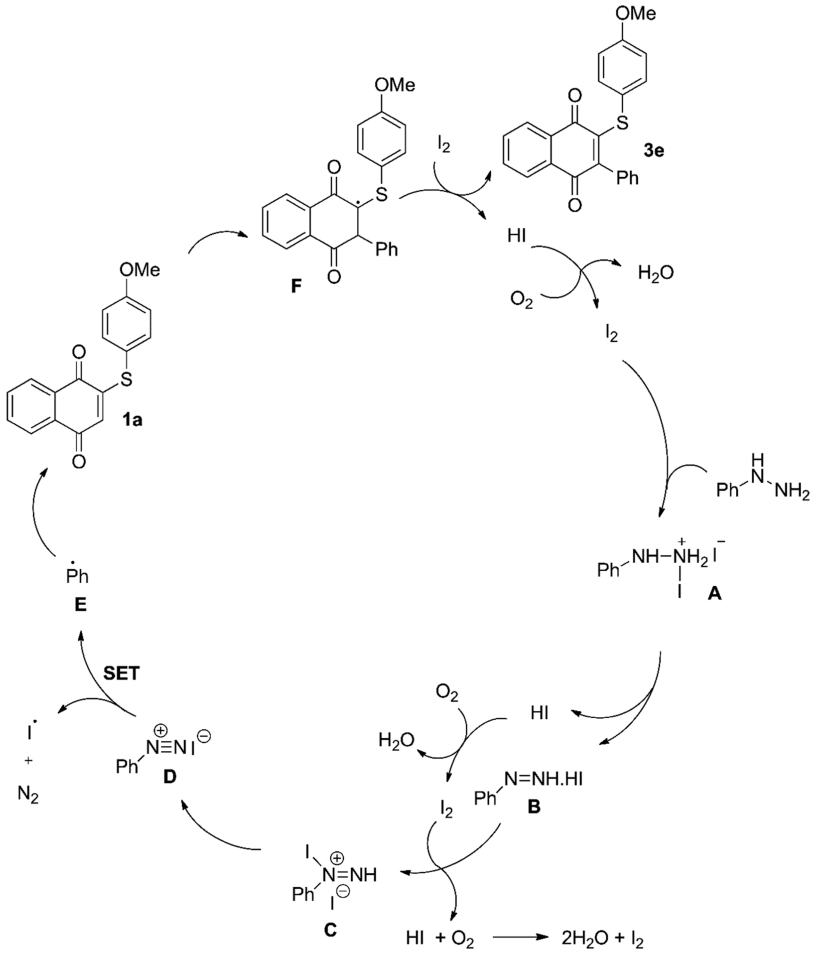
Scheme 5. Mechanism of Iodine-Catalyzed Arylation of Substituted 1,4-Napthoquinone



diazonium salt **D**, which underwent a single electron transfer (SET) and nitrogen release to afford the phenyl radical **E** and the iodine radical. Formation of the radical adduct **F** between **E** and **1a** followed by a single electron oxidation with iodine molecule leads to the formation of **3e** via a radical cation (Scheme 5).

CONCLUSIONS

Herein, we have demonstrated a metal- and base-free generation of aryl radicals from aryl hydrazines via catalytic molecular iodine under air at 40 °C in TFE. The reaction is reproducible and consistent with a variety of aryl hydrazines. This strategy is harnessed to arylate substituted 1,4-naphthoquinones. Through this protocol, a library of diversely substituted 2- or 3-arylated-1,4-naphthoquinones were accessed in moderate to excellent yield. The putative mechanism depicted in this report is the result of meticulously executed control experiments, which indicated that the molecular iodine reduces to hydroiodic acid during the reaction and gets oxidized back in the presence of air to sustain the catalytic cycle, which, in turn, generates the aryl radical from aryl hydrazine. Further application of this methodology for arylating key organic building blocks is presently ongoing in our lab.

EXPERIMENTAL SECTION

General. All reactions were carried out under air as specified. The reaction was monitored by thin-layer chromatography (TLC, silica gel 60 F_{254}), using ultraviolet (UV) light to visualize the course of the reaction. **1a−e** were experimentally synthesized, whereas **1f−h** and **2a−d** were procured from multiple commercial vendors. ^{1}H NMR and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal standard at ambient temperature unless otherwise indicated with Bruker 400 MHz instruments at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectroscopy. Splitting patterns are designated as singlet (s), doublet (d), triplet (t), and doublet of doublet (dd). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Mass spectrometry analysis was done with a 6540 UHD Accurate-Mass QTOF liquid chromatography−mass spectrometry (LC−MS) system (Agilent Technologies) equipped with an Agilent 1290 LC system procured by the Department of Chemistry, School of Natural Sciences, Shiv Nadar University, Uttar Pradesh 201314, India.

Representative Synthesis of 2-Thioaryl Derivatives of 1,4-Naphthoquinone (1a−c). In a 25 mL Schlenk tube, 1,4-naphthoquinone (200 mg, 1.26 mmol), 4-methoxythiophenol (177.31 mg, 1.26 mmol), and copper iodide (CuI) (47.99 mg, 0.252 mmol) were dissolved in dimethylformamide (DMF) (2 mL), and then the tube was covered and stirred at 100 °C for 10 h under an O_2 balloon. After the reaction, the mixture was diluted with saturated saline solution and extracted with ethyl acetate (EtOAc). The organic layer was collected and dried by anhydrous sodium sulfate (Na_2SO_4). The residue was purified by column chromatography on silica gel using an EtOAc/hexane mixture as the eluent to afford the pure product.

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*2-((4-Methoxyphenyl)thio)naphthalene-1,4-dione (**1a**).* Following the general procedure, the desired compound was prepared in 90% yield as a yellow crystalline solid. The eluent was EtOAc/*n*-hexane (10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.12 (m, 1H), 8.03−8.00 (m, 1H), 7.73−7.70 (m, 2H), 7.45−7.42 (m, 2H), 7.02−7.00 (m, 2H), 6.09 (s, 1H), 3.87 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.5, 182.2, 161.6, 157.6, 137.3, 134.4, 133.4, 128.3, 126.9, 126.6, 117.6, 116.1, 55.6. HRMS (ESI+) *m*/*z* calcd. for $C_{17}H_{12}O_3S$ $[M + H]^+$: 297.0580, found: 297.0595.

*2-(Phenylthio)naphthalene-1,4-dione (**1b**).* Following the general procedure, the desired compound was prepared in 85% yield as a yellow crystalline solid. The eluent was EtOAc/*n*-hexane (10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.13 (m, 1H), 8.03−8.01 (m, 1H), 7.76−7.69 (m, 2H), 7.56−7.50 (m, 5H), 6.12 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.3, 182.1, 156.8, 135.9, 134.5, 133.5, 132.4, 131.9, 130.7, 130.5, 128.3, 127.5, 127.0, 126.7. HRMS (ESI+) *m*/*z* calcd. for $C_{16}H_{10}O_2S$ $[M + H]^+$: 267.0474, found: 267.0490.

*2-((4-Fluorophenyl)thio)naphthalene-1,4-dione (**1c**).* Following the general procedure, the desired compound was prepared in 84% yield as a yellow crystalline solid. The eluent was EtOAc/*n*-hexane (10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.13 (dd, *J* = 8 Hz, 1H), 8.04−8.02 (dd, *J* = 8 Hz, 1H), 7.78−7.70 (m, 2H), 7.55−7.52 (m, 2H), 7.23−7.19 (t, *J* = 8 Hz, 1H), 6.07 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.2, 182.0, 165.6, 163.0, 156.7, 138.1, 138.0, 134.6, 133.6, 132.3, 131.8, 128.4, 127.0, 126.7, 122.8, 118.0, 117.8. HRMS (ESI+) *m*/*z* calcd. for $C_{16}H_9FO_2S$ $[M + H]^+$: 285.0380, found: 285.0389

Representative Synthesis of 2-Amino Derivatives of 1,4-Naphthoquinone (1d−e). A mixture of 1,4-naphthoquinone (158 mg, 1 mmol), *N*-methylbenzyl amine (60.59 mg, 0.5 mmol), iodine (12.7 mg, 0.05 mmol), and anhydrous ethanol (EtOH) (2 mL) was irradiated with ultrasound in an open vessel at room temperature until the disappearance of the starting material (40 min, checked by TLC). The residue was washed with saturated saline solution and extracted with dichloromethane (DCM). The extracts were dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel using an EtOAc/hexane mixture as the eluent to afford the pure product.

*2-(Piperidin-1-yl)naphthalene-1,4-dione (**1d**).* Following the general procedure, the desired compound was prepared in 84% yield as a deep red amorphous solid. The eluent was EtOAc/*n*-hexane (10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.96 (m, 2H), 7.69−7.59 (m, 2H), 6.01 (s, 1H), 3.48−3.39 (m, 4H), 1.71 (s, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 183.7, 183.5, 154.3, 133.9, 132.4, 126.7, 125.6, 110.5, 50.6, 25.9, 24.4. HRMS (ESI+) *m*/*z* calcd. for $C_{15}H_{15}NO_2$ $[M + H]^+$: 242.1176, found: 242.1203.

*2-(Benzyl(methyl)amino)naphthalene-1,4-dione (**1e**).* Following the general procedure, the desired compound was prepared in 87% yield as a deep red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8 Hz, 1H), δ 8.01 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 8 Hz, 1H), 7.64 (t, *J* = 8 Hz, 1H), 7.39−7.28 (m, 5H), 5.97 (s, 1H), 4.88 (s, 2H), 3.06 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 183.6, 183.3, 152.6, 134.1, 132.8, 132.3, 128.9, 127.7, 127.3, 126.8, 125.6, 108.4, 57.6, 40.3. HRMS (ESI+) *m*/*z* calcd. for $C_{18}H_{15}NO_2$ $[M + H]^+$: 278.1176, found: 278.1180.

*Representative Synthetic Procedure for Arylation of Unsubstituted or Substituted 1,4-Naphthoquinone (**3a**−**3s**).* An oven-dried round-bottom flask, equipped with a magnetic stir bar, was charged with 1,4-naphthoquinone (100 mg, 0.63 mmol), phenyl hydrazine (136.26 mg, 1.26 mmol), and iodine (48.14 mg, 0.19 mmol) in 2,2,2-trifluoroethanol (TFE) (4 mL) and allowed to stir at 40 °C under air for 20 h. The solvent was removed under reduced pressure. The residue was washed with saturated saline solution and extracted with ethyl acetate (EtOAc). The extracts were dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel using an EtOAc/hexane mixture as the eluent to afford the pure product.

*2-((4-Fluorophenyl)thio)-3-(4-methoxyphenyl)-naphthalene-1,4-dione (**3a**).* Following the general procedure, the desired compound was prepared in 84% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.12 (dd, *J* = 8 Hz, 1H), 8.05−8.03 (dd, *J* = 8 Hz, 1H), 7.77−7.70 (m, 2H), 7.23−7.16 (m, 4H), 6.91−6.83 (m, 4H), 3.84 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.4, 160.4, 147.3, 134.2, 134.2, 133.8, 132.8, 131.7, 127.2, 127.0, 125.7, 116.3, 116.0, 113.6, 55.5. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{15}FO_3S$ $[M + H]^+$: 391.0799, found: 391.0798.

*2-(4-Methoxyphenyl)-3-(phenylthio)naphthalene-1,4-dione (**3b**).* Following the general procedure, the desired compound was prepared in 86% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.13 (dd, *J* = 8 Hz, 1H), 8.05−8.03 (dd, *J* = 8 Hz, 1H), 7.77−7.69 (m, 2H), 7.24−7.20 (m, 4H), 7.17−7.15 (m, 3H), 6.91−6.89 (m, 2H), 3.84 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.5, 181.6, 160.4, 148.0, 147.0, 134.1, 134.1, 133.8, 132.9, 131.8, 131.5, 129.0, 127.5, 127.1, 127.0, 125.8, 113.5, 55.5. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{16}O_3S$ $[M + H]^+$: 373.0893, found: 373.0908.

*2-((4-Fluorophenyl)thio)-3-phenylnaphthalene-1,4-dione (**3c**).* Following the general procedure, the desired compound was prepared in 90% yield as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.13 (m, 1H), 8.04−8.02 (m, 1H), 7.77−7.70 (m, 4H), 7.55−7.52 (m, 3H), 7.23−7.19 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.2, 182.1, 165.6, 163.0, 156.7, 138.1, 138.0, 134.6, 133.6, 132.3, 131.8, 129.8, 128.4, 127.0, 126.8, 122.8, 118.0, 117.8. HRMS (ESI+) *m*/*z* calcd. for $C_{22}H_{13}FO_2S$ $[M + H]^+$: 361.0693, found: 361.0711.

*2-Phenyl-3-(phenylthio)naphthalene-1,4-dione (**3d**).* Following the general procedure, the desired compound was prepared in 85% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.12 (m, 1H), 8.06−8.01 (m, 1H), 7.75−7.71 (m, 2H), 7.55−7.51 (m, 3H), 7.36−7.35 (m, 2H), 7.24−7.20 (m, 3H), 7.16−7.14 (m, 2H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.2, 181.6, 156.8, 148.2, 147.8, 135.9, 134.5, 134.2, 133.8, 133.7, 133.5, 132.7, 132.2, 131.7, 130.7, 130.5, 129.8, 129.0, 129.0, 128.3, 128.0, 127.6, 127.1, 127.0, 126.7. HRMS (ESI+) *m*/*z* calcd. for $C_{22}H_{14}O_2S$ $[M + H]^+$: 343.0787, found: 343.0803.

*2-((4-Methoxyphenyl)thio)-3-phenylnaphthalene-1,4-dione (**3e**).* Following the general procedure, the desired compound was prepared in 88% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.10 (m, 1H), 8.06−8.04 (m, 1H), 7.74−7.71 (m, 2H), 7.36−7.33 (m, 3H), 7.20−7.14 (m, 4H), 6.69−6.65 (m, 2H), 3.75 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.3, 182.0, 159.6, 149.0, 147.9, 146.8, 134.5, 134.1, 133.7, 132.7, 132.3, 129.9, 128.9, 128.0, 127.0,

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127.0, 123.6, 114.7, 55.4. HRMS (ESI+) m/z calcd. for $C_{23}H_{16}O_3S$ $[M + H]^+$: 373.0893, found: 373.0898.

*2-(4-Methoxyphenyl)-3-((4-methoxyphenyl)thio)-naphthalene-1,4-dione (**3f**).* Following the general procedure, the desired compound was prepared in 90% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.10 (m, 1H), 8.04−8.02 (m, 1H), 7.75−7.67 (m, 2H), 7.16 (d, J = 8 Hz, 4H), 6.89 (d, J = 8 Hz, 2H), 6.68 (d, J = 8 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.5, 182.0, 160.3, 159.6, 148.2, 146.4, 134.2, 134.0, 133.7, 132.8, 132.4, 132.3, 131.7, 127.0, 126.9, 125.8, 123.9, 114.6, 113.4, 55.4. HRMS (ESI+) m/z calcd. for $C_{24}H_{18}O_4S$ $[M + H]^+$: 403.0999, found: 403.0982.

*2-(3-Fluorophenyl)-3-((4-methoxyphenyl)thio)-naphthalene-1,4-dione (**3g**).* Following the general procedure, the desired compound was prepared in 85% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.07 (m, 2H), 7.77−7.71 (m, 2H), 7.30−7.27 (m, 1H), 7.13−7.10 (m, 2H), 7.02−6.92 (m, 2H), 6.83−6.80 (m, 1H), 6.67−6.65 (m, 2H), 3.76 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.1, 181.9, 161.1, 159.9, 150.2, 144.6, 134.9, 134.3, 133.8, 132.5, 132.2, 129.6, 129.5, 127.1, 127.0, 125.6, 125.6, 122.7, 117.2, 117.0, 115.7, 115.5, 114.8, 55.5. HRMS (ESI+) m/z calcd. for $C_{23}H_{15}FO_3S$ $[M + H]^+$: 391.0799, found: 391.0806.

*2-(4-Methoxyphenyl)-3-(piperidin-1-yl)naphthalene-1,4-dione (**3h**).* Following the general procedure, the desired compound was prepared in 66% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.03 (m, 2H), 7.69−7.62 (m, 2H), 7.20−7.18 (m, 2H), 6.97−6.94 (m, 2H), 3.85 (s, 3H), 2.92 (t, J = 4 Hz, 4H), 1.64−1.53 (m, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 184.4, 183.9, 158.9, 151.7, 133.8, 132.7, 132.6, 132.4, 132.0, 127.6, 126.8, 126.2, 126.2, 113.5, 55.4, 53.6, 26.6, 24.2. HRMS (ESI+) m/z calcd. for $C_{22}H_{21}NO_3$ $[M + H]^+$: 348.1594, found: 348.1655.

*2-Phenyl-3-(piperidin-1-yl)naphthalene-1,4-dione (**3i**).* Following the general procedure, the desired compound was prepared in 69% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.05 (m, 2H), 7.72−7.64 (m, 2H), 7.43 (t, J = 8 Hz, 2H), 7.34−7.31 (m, 1H), 7.28−7.27 (m, 2H), 2.93 (t, J = 4 Hz, 4H), 1.63−1.54 (m, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 184.4, 183.6, 152.0, 135.5, 133.9, 132.7, 132.6, 132.8, 130.9, 128.0, 127.5, 126.8, 126.3, 53.7, 26.6, 24.2. HRMS (ESI+) m/z calcd. for $C_{21}H_{19}NO_2$ $[M + H]^+$: 318.1489, found: 318.1543.

*2-(Benzyl(methyl)amino)-3-(4-methoxyphenyl)-naphthalene-1,4-dione (**3j**).* Following the general procedure, the desired compound was prepared in 71% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, J = 8 Hz, 2H), 7.72−7.65 (m, 2H), 7.35−7.24 (m, 5H), 7.10 (d, J = 8 Hz, 2H), 6.90 (d, J = 8 Hz, 2H), 4.31 (s, 2H), 3.84 (s, 3H), 2.50 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ184.5, 183.9, 159.1, 151.7, 137.3, 133.9, 132.7, 132.6, 132.4, 132.1, 128.6, 128.4, 127.6, 127.5, 126.3, 126.2, 113.5, 59.7, 55.4, 42.1. HRMS (ESI+) m/z calcd. for $C_{25}H_{21}NO_3$ $[M + H]^+$: 384.1594, found: 384.1602.

*2-(Benzyl(methyl)amino)-3-phenylnaphthalene-1,4-dione (**3k**).* Following the general procedure, the desired compound was prepared in 75% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.75−7.67 (m, 2H), 7.40−7.28 (m, 8H), 7.21−7.19 (m, 2H), 4.34 (s, 2H), 2.49 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 184.5, 183.5, 151.9, 137.2, 135.2, 133.9, 132.7, 132.6, 132.3, 130.9, 128.6, 128.4, 127.9, 127.6, 127.5, 126.4, 126.2, 59.7, 42.1. HRMS (ESI+) m/z calcd. for $C_{24}H_{19}NO_2$ $[M + H]^+$: 354.1489, found: 354.1495.

*2-Bromo-3-phenylnaphthalene-1,4-dione (**3l**).* Following the general procedure, the desired compound was prepared in 55% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42−8.26 (m, 2H), 7.98−7.95 (m, 2H), 7.75−7.66 (m, 3H), 7.52−7.41 (m, 2H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 182.6, 181.7, 149.9, 140.5, 139.3, 135.4, 134.6, 134.3, 134.2, 129.3, 128.3, 127.7, 127.5, 127.2, 127.0, 126.8, 126.1. HRMS (ESI+) m/z calcd. for $C_{16}H_9BrO_2$ $[M + H]^+$: 312.9859, found: 312.9852.

*2-Bromo-3-(4-methoxyphenyl)naphthalene-1,4-dione (**3m**).* Following the general procedure, the desired compound was prepared in 61% yield as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.10 (m, 2H), 7.79−7.76 (m, 2H), 7.58 (d, J = 8 Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 7.05−6.99 (m, 2H), 3.88 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 181.9, 178.5, 161.5, 160.6, 149.4, 147.6, 134.4, 134.2, 133.9, 133.9, 131.3, 131.2, 127.6, 127.6, 127.2, 126.0, 114.2, 113.6, 55.5. HRMS (ESI+) m/z calcd. for $C_{17}H_{11}BrO_3$ $[M + H]^+$: 342.9964, found: 342.9971.

*2-(4-Methoxyphenyl)-3-methylnaphthalene-1,4-dione (**3n**).* Following the general procedure, the desired compound was prepared in 63% yield as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.10 (m, 2H), 8.03−8.00 (m, 1H), 7.76−7.72 (m, 2H), 7.32−7.29 (d, J = 12 Hz, 1H), 7.19−7.17 (d, J = 8 Hz, 2H), 7.01−6.97 (m, 2H), 3.86 (s, 3H), 2.12 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 186.0, 184.6, 159.9, 145.9, 144.0, 134.5, 134.4, 133.7, 133.6, 131.1, 127.5, 126.8, 126.3, 114.0, 113.8, 55.5, 14.9. HRMS (ESI+) m/z calcd. for $C_{18}H_{14}O_3$ $[M + H]^+$: 279.1016, found: 279.1014.

*2-(2,4-Dinitrophenyl)naphthalene-1,4-dione (**3o**).* Following the general procedure, the desired compound was prepared in 74% yield as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 2H), 8.59 (dd, J = 4 Hz, 4H), 7.82 (t, J = 8 Hz, 2H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 130.9, 129.0, 119.3. HRMS (ESI+) m/z calcd. for $C_{16}H_8N_2O_6$ $[M + H]^+$: 325.0455, found: 325.0086.

*2-(4-Methoxyphenyl)naphthalene-1,4-dione (**3p**).* Following the general procedure, the desired compound was prepared in 66% yield as an orange amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (m, 1H), 8.12−8.09 (m, 1H), 7.77−7.75 (m, 2H), 7.58 (d, J = 8 Hz, 2H), 7.04 (s, 1H), 6.99 (d, J = 8 Hz, 2H), 3.87 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 185.3, 185.0, 161.5, 147.6, 133.9, 133.9, 133.9, 132.7, 132.3,131.2, 127.2, 126.0, 125.8, 114.2, 55.5. HRMS (ESI+) m/z calcd. for $C_{17}H_{12}O_3$ $[M + H]^+$: 265.0859, found: 265.0845.

*2-Phenylnaphthalene-1,4-dione (**3q**).* Following the general procedure, the desired compound was prepared in 23% yield as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (m, 1H), 8.10−8.08 (m, 1H), 7.80−7.75 (m, 2H), 7.59−7.56 (m, 1H), 7.49−7.47 (m, 1H), 7.24−7.22 (m, 2H), 7.09−7.06 (m, 1H), 6.98 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 185.2, 184.9, 148.3, 145.9, 138.8, 135.4, 134.1, 134.0, 133.5, 133.4, 132.6, 132.3, 132.2, 132.0, 130.6, 130.2, 129.6, 128.6, 128.4, 127.8, 127.2, 126.8, 126.6, 126.1. HRMS (ESI+) m/z calcd. for $C_{16}H_{10}O_2$ $[M + H]^+$: 235.0754, found: 235.0788.

*2,3-Diphenylnaphthalene-1,4-dione (**3r**).* Following the general procedure, the desired compound was prepared in 65% yield as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (m, 1H), 8.13−8.08 (m, 2H), 7.79−7.75 (m, 3H), 7.59−7.56 (m, 3H), 7.49−7.47 (m, 3H), 7.08 (s, 1H), 6.98 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 185.3, 184.5,

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148.3, 138.8, 135.4, 134.8, 134.04, 133.9, 133.5, 132.6, 132.2, 130.2, 129.6, 128.6, 127.2, 126.6, 126.1. HRMS (ESI+) m/z calcd. for $C_{22}H_{14}O_2$ $[M + H]^+$: 311.1067, found: 311.1114.

*2-(4-Methoxyphenyl)-3-phenylnaphthalene-1,4-dione (**3s**).* Following the general procedure, the desired compound was prepared in 82% yield as an orange amorphous solid. ^{1}H N14MR (400 MHz, $CDCl_3$) δ 8.23−8.17 (m, 2H), 7.80−7.78 (m, 2H), 7.27 (d, J = 4 Hz, 3H), 7.12−7.10 (m, 2H), 7.04−7.02(m, 2H), 6.77 (d, J = 8 Hz, 2H), 3.78 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 185.2, 184.9, 159.6, 145.4, 145.3, 133.9, 133.9, 132.4, 130.7, 128.2, 127.8, 126.7, 126.7, 125.4, 113.3, 55.3. HRMS (ESI+) m/z calcd. for $C_{23}H_{16}O_3$ $[M + H]^+$: 341.1172, found: 341.1168.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b04014.

Control experiments; ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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