

Photochemical C–H Arylation of Naphthoquinones Using Eosin Y

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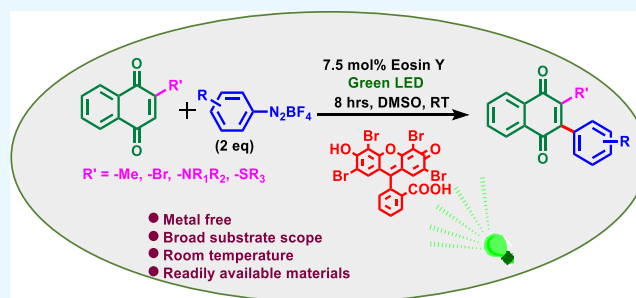
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ABSTRACT: A visible-light-mediated C–H arylation of substituted 1,4-naphthoquinones (1,4-SNQ) and 1,2-naphthoquinone (1,2-NQ) with diazonium salt using a photocatalyst eosin Y at room temperature in a single step (isolated yield of $\geq 75\%$) is described in this report. The rate-determining step of the reaction is aryl radical generation, which was trapped by high-resolution mass spectrometry. Cost-effectiveness, operational simplicity, a short reaction time, high atom economy, and a good yield make this photoredox-mediated process a valuable alternative to the transition-metal (Fe, Cu, Pd, etc.)-catalyzed reaction.



INTRODUCTION

Naphthoquinones have manifold activities such as antibiotic, antifungal, anti-inflammatory, anti-allergic, apoptotic, and antithrombic agents and play a significant role in the proton-coupled electron transfer mechanism in biological processes.¹ Arylated naphthoquinones constitute an exclusive class of natural products, embedded in crismicin A, microphyllaquinone, conocurvone and angelmicin B, δ -rubromycin, and in some other natural products (Figure 1).^{2a} Potent inhibitory effect of naphthoquinone derivatives against heat shock protein 90 (Hsp90) is also well understood.^{2b,c} However, there are very few efficient synthetic protocols of arylated naphthoquinones in the literature.^{3a} A few general strategies include transition-metal-catalyzed cross-coupling reactions through C–H bond activation, cycloaddition ring construction and hypervalent iodine-based oxidation and so forth (Scheme 1).^{2a,3} The common barrier of most of these methods are inevitable use of transition metals that is costly and produces toxic metal waste in the environment. On the other hand, quinones can act as both ligands and oxidants in reactions, and therefore, it is difficult for quinones to be a substrate in transition-metal-catalyzed reactions. Therefore, the reasonable yield of arylated naphthoquinone via a metal-free catalyst is highly preferable in both synthetic and medicinal chemistry.

In recent years, visible-light-mediated photoredox catalysis using a metal-free organic dye has become a powerful strategy for activating small molecules via the single-electron transfer (SET) process. It allows many previously unachievable transformations.^{4a} The use of visible light is inexpensive and non-polluting to initiate organic changes. The other significant advantage of this procedure is its operational simplicity, short reaction time, high atom economy, and excellent yield. The well-known visible-light photoredox catalysts include ruthenium and iridium polypyridyl complexes and organic dyes, which efficiently convert visible light into chemical energy

under mild conditions.^{4a} Despite the excellent photocatalytic properties of metal (Ru and Ir)-based photocatalyst in organic synthesis, they are usually expensive and potentially toxic.⁵ In contrast, organic dyes are inexpensive, less harmful, and easier to handle. Moreover, the structural diversity of organic dyes and their different redox and photochemical properties are beneficial for developing new photocatalysts. Recently, various fluorescein dyes such as eosin Y (EY) have been utilized successfully as a photoredox catalyst in various organic transformations.⁵ After photoexcitation, the triplet excited state of EY (EY*) undergoes reductive or oxidative quenching by accepting or donating an electron to produce a radical anion or radical cation, respectively.^{4,5} In 2012, König research group reported EY-catalyzed photochemical C–H activation of heteroarenes with aryl diazonium salts, which was a metal-free Meerwein arylation.⁶ Herein, we would like to report an EY-mediated metal-free Meerwein C(3)-H arylation of substituted 1,4-naphthoquinones (1,4-SNQ) and 1,2-naphthoquinone (1,2-NQ) with aryl diazonium salts in the presence of green light at room temperature (RT) (Scheme 1).

RESULTS AND DISCUSSION

Initially, to optimize the reaction condition, we took *p*-methoxyphenyl diazonium tetrafluoroborate salt (2g) as a source of aryl group and menadione (1b) as a model compound for substituted naphthoquinone with EY as a photocatalyst in the presence of Green LED, with solvent dimethyl sulfoxide (DMSO) (5 mL) (Table 1). It was

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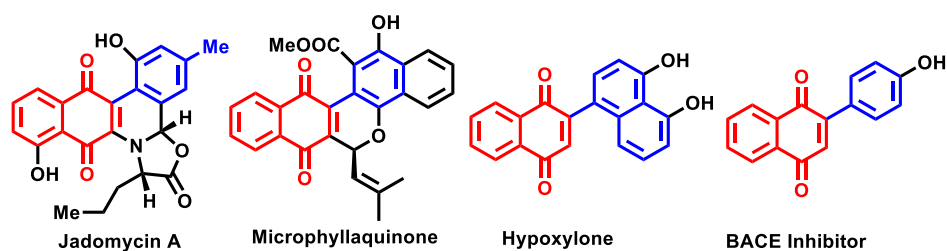


Figure 1. Selected biologically active arylated quinone derivatives.

Scheme 1. Arylation of Substituted Naphthoquinones: (a) Pd Catalyzed; (b) Metal Reagents Catalyzed; (c) Iodine Catalyzed; (d) Transition-Metal-Free; (e) Using Boronic Acid; and (f) EY Mediated (Present Work)

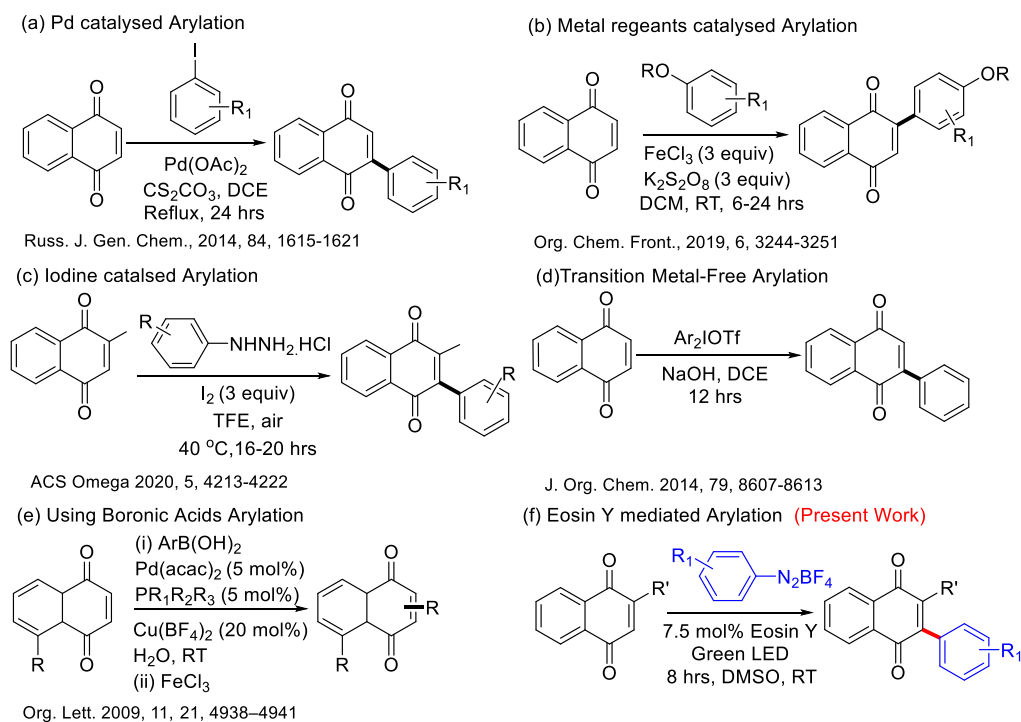


Table 1. Optimization of Reaction Conditions^a

entry	EY (mol %)	[Ru(bipy) ₃] ²⁺	solvent	isolated yield (%)
1	2.0	—	DMSO	58
2	5.0	—	DMSO	70
3	7.5	—	DMSO	90
4 ^b	7.5	—	DMSO	75
5	7.5	—	DMSO-H ₂ O	—
6	7.5	—	CH ₃ CN	—
7	7.5	—	MeOH	30
8 ^c	7.5	—	DMSO	91
9 ^d	7.5	—	DMSO	—
10 ^e	—	—	DMSO	—
11	—	7.5	DMSO	85

^aReaction conditions (unless otherwise specified): menadione (1 mmol), *p*-methoxyphenyl diazonium tetrafluoroborate (2 mmol), solvent (5 mL), EY: 7.5 mol %, irradiation under an air atmosphere at RT using green LED; reaction completed within 8 h. ^bBlue LED. ^cIn a N₂ atmosphere. ^dIn the absence of green light. ^eIn the absence of EY.

observed that both components and EY are extremely highly soluble in DMSO aprotic solvent. Using 2 mol % EY and irradiation with green light, arylated product 2-(4-methoxyphenyl)-3-methylnaphthalene-1,4-dione (**3f**) was obtained in

~58% yield at RT in DMSO after 8 h in the presence of air (entry 1). After increasing the amount of photocatalyst EY from 2.0 to 7.5 mol %, we observed a significant increase in the product yield from 58 to 90% (entry 3). A reaction was also carried out in the presence of blue LED; however, product yields were around 75% only (entry 4). In presence of a green light source, reactions were monitored in various solvents [DMSO, acetonitrile, MeOH, DMSO/H₂O (1:1); entry 5–7]. The result showed that acetonitrile (CH₃CN) did not give the desired product (entry 7). In the presence of N₂ or an inert environment, 91% yield was found (entry 8). Meanwhile, without a photocatalyst or light, the desired product was not found (entries 9 and 10). We conducted the reaction with well-known tris(bipyridine)ruthenium(II) chloride as the photoredox catalyst and an 85% isolated yield was observed.

After optimizing the reaction condition, we explored the substrate scope of the reaction over the various 1,4-SNQ (**1a–1i**) and substituted 1,2-naphthoquinone 1,2-SNQ (**1j–1k**) in the presence of 7.5 mol % EY with various aryl diazonium tetrafluoroborates (**2a–2h**). All the 1,4-SNQ and 1,2-NQ were arylated in good to excellent yields (isolated yield: ≥ 75%, Figure 2). We have isolated a more arylated product for 1,4-SNQ having a functional group of +R effect with less steric hindrance at the 2 position (Figure S4). Arylation of 1,4

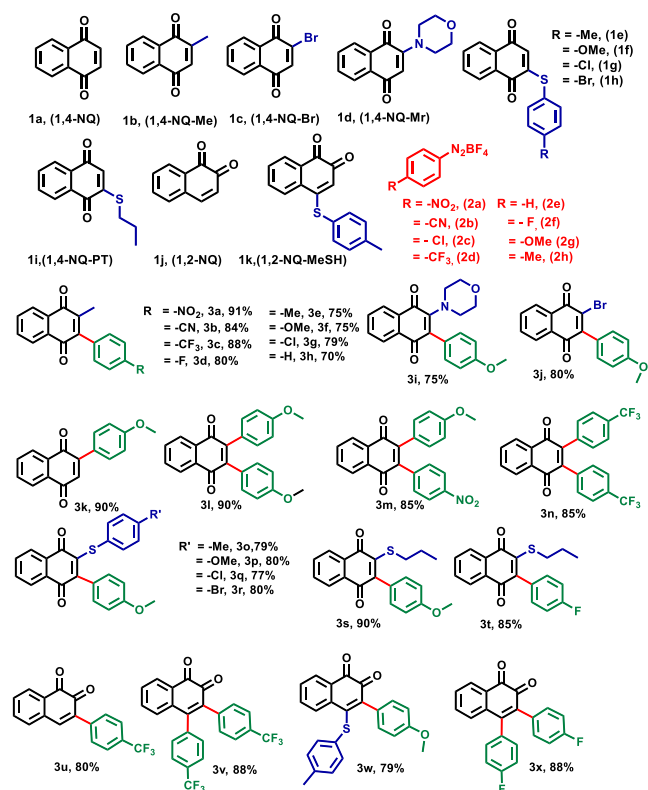


Figure 2. Possible arylation of 1,4-SNQ (1a–1i) and substituted 1,2-naphthoquinone (1,2-SNQ) (1j–1k) with substituted diazonium salts (2a–2h) along yield.

benzoquinone, gives the mixture of products (mono-, di-, tri-, and tetra-substituted) according to the high-resolution mass spectroscopy (HRMS) study (Figure S5). A combination of 1-dimensional and 2-dimensional NMR experiments revealed that arylation occurred at the 3 position of 1,2-NQ (3u) (Supporting Information page no. S59–S61). To highlight the utility of the method, the reaction was also carried out on a relatively large scale (1 mmol scale) with 1b and 2b in 5 mL of DMSO (condition: 7.5 mol % EY, RT, 12 h) and ~85% yield (isolated) was observed.

Kinetic studies revealed that the aryl diazonium salts ($\text{ArN}_2^+\text{BF}_4^-$) with electron-withdrawing groups (EWGs), for example, $-\text{NO}_2$ and $-\text{CN}$ and so forth at the para-position of diazonium group, arylation of 1b was completed in less time compared to diazonium salts with electron-donating groups (EDGs) such as $-\text{Me}$ and $-\text{OMe}$ at the same position (Table 2 and Figure S1). This result suggested that oxidative quenching of EY is initiated by the transfer of electrons from the ArN_2^+ to the EY^* , that is, triplet excited state of EY (-1.11 V vs SCE for EY^* to EY^{\bullet}).⁷ EWG increases the reduction potential (Table 2)⁸ of ArN_2^+ which may favor the electron transfer process from EY^* to EY^{\bullet} . Due to the presence of EDG, a lower reduction potential is observed (Table 2);⁸ for that reason, the electron transfer rate from EY^* is anticipated to be slower. A fluorescence quenching experiment (Figure S2) revealed that $\text{ArN}_2^+\text{BF}_4^-$ is efficiently quenching EY^* and the Stern–Volmer quenching constant value (K_{SV}) (e.g., 2.2 for 2e, Tables 2 and S1 and Figure S2) was higher in comparison to 1,4-SNQ or 1,2-NQ (e.g., 0.058 for 1b)⁹ and thereby participation of ArN_2^+ in the SET process is more justified. The rate of the reaction of various substituted $\text{ArN}_2^+\text{BF}_4^-$ with 1b was followed by a linear free-energy relationship (Hammett

Table 2. Effect of the Substituent of the Aryl Diazonium Salt on the Reaction Rate with 1b; Correlation of E_{red}/V of Aryl Diazonium Salt vs SCE; and Stern–Volmer Quenching Constant (K_{SV})

substrate	E_{red}^a/V	K_{SV}^b	rate ^c /mM min ⁻¹
$-\text{NO}_2$ (2a)	0.20	8.5	14.6×10^{-2}
$-\text{CN}$ (2b)	0.16	6.4	8.7×10^{-2}
$-\text{Cl}$ (2c)	0.010 ^c	3.5	6.6×10^{-2}
$-\text{H}$ (2e)	-0.10	2.2	5.9×10^{-2}
$-\text{CH}_3$ (2h)	-0.16	0.92	3.9×10^{-2}

^aReduction potential of 2c is determined in CH_3CN using *n*-BuBF₄ as electrolyte (0.1 M) vs SCE. E_{red}/V of other diazonium salts are from ref 8 in similar conditions. ^bStern–Volmer quenching constant (K_{SV}) was determined via a steady-state fluorescence quenching experiment. ^cAll the rate constants reported in Table 2 were determined using HPLC (Figure S1). Experimental detail is given in the Supporting Information.

plot). It supports that the reaction is responsive to the presence of EDG and EWG on para-substituted aryl diazonium salts (Figure 3). The rate (mM min⁻¹) and K_{SV} as a function of E_{red} (V) displayed that EY^* is quenched faster by substituted ArN_2^+ having a higher E_{red} value (Figure S3).

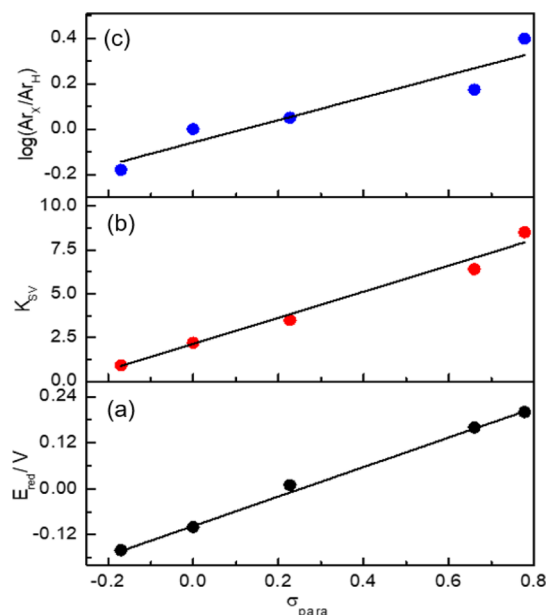


Figure 3. (a) Correlation E_{pa} with σ_{para} ; (b) correlation of K_{SV} with the Hammett parameter (σ_{para}); and (c) Hammett plot for 1,4-SNQ.

Based on our experimental result and similar mechanisms reported in the literature, it is concluded that the initially formed singlet photoexcited state of EY ($\tau_{\text{S}} = 6 \pm 2$ ns) transforms to its triplet photoexcited state (EY^*) ($\tau_{\text{T}} = 320 \pm 10$ ns) via a facile intersystem crossing ($\tau_{\text{isc}} = 6 \pm 2$ ns in acetonitrile) (Figure 4).¹⁰ A single electron transfer from EY^* to diazonium salts generated an aryl radical (Ar^{\bullet}) and EY^{\bullet} (oxidative quenching of EY^*). Ar^{\bullet} readily reacts with the quinone moiety and produces $[\text{1,4-SNQ-Ar}]^{\bullet}$ adduct. It was found that the reaction was quenched by the TEMPO and an adduct product of TEMPO with Ar^{\bullet} was detected by the HRMS technique (Figure S4). We are proposing that the photoredox cycle can be completed via electron transfer from $[\text{1,4-SNQ-Ar}]^{\bullet}$ to EY^{\bullet} . Moreover, a kinetic study revealed

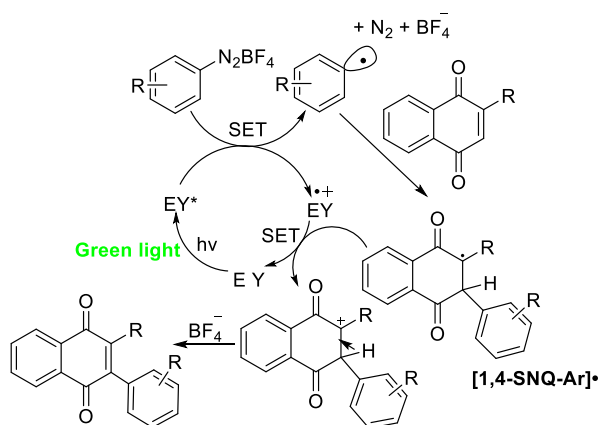


Figure 4. Proposed mechanism for the arylation of 1,4-SNQ and 1,2-NQ with aryl diazonium salts.

that the yield and the rate of the reaction are unaffected if the reaction is conducted in a N_2 atmosphere. It confirms that O_2 is not involved in the photoredox catalytic cycle. Plausible reaction mechanism is described in Figure 4.

In summary, we have developed a cost-effective, metal-free visible-light-mediated one-step procedure of synthesising arylated derivatives of 1,4-SNQ in DMSO with a very good yield (isolated yield: $\geq 75\%$) at RT. Notably, the catalytic system is also possible for the 1 mmol scale, $\sim 85\%$ yield was observed for **1b** with **2b**. The reaction proceeds through the formation of aryl radical and an adduct product of TEMPO with Ar^\bullet was detected by the HRMS technique. We believe this method can be beneficial for replacing the transition-metal-catalyzed arylation of 1,4-SNQ and 1,2-SNQ.

EXPERIMENTAL SECTION

General Information. All the commercially available compounds were supplied by Sigma-Aldrich and Alfa Aesar and used directly in the reaction. Thin-layer chromatography (TLC) was done on an aluminum plate coated with SiO_2 (Merck 60, F-254 MS grade) to monitor the progress of reactions. Arylated naphthoquinone product was purified using flash column chromatography on silica gel (200–300 mesh) with a mixture of hexane and ethyl acetate (9:2 v/v). Using tetramethylsilane (0.00 ppm) as an internal standard, 1H and $^{13}C\{^1H\}$ NMR spectra were recorded at an ambient temperature with Bruker instruments at 400 MHz and 100 MHz, respectively. HRMS was performed using an Agilent 6540 UHD accurate-mass quadrupole time-of-flight mass spectrometer equipped with the Agilent 1290 UPLC system. Steady-state fluorescence quenching experiment was carried out in a spectrofluorometer (FSS, Edinburgh) at RT. High-performance liquid chromatography (HPLC) experiments were carried out using a Waters Alliance System (Milford, MA) with an e2695 separation module and a 2998 PDA (photodiode-array) detector.

Photoreactor Setup. All the reactions were performed in the side irradiated glass vial using an in-house built photoreactor (5630/5730 Green LED, 1.5 W/module, pack of 20 modules; lamp luminous efficiency (lm/W): 110lm/W, Multi-use, Ip Rating: IP65, waterproof, forward voltage: 12 V, Brand: K3, country of origin: India) which was reported in our previous work.⁹

Synthesis of Diazonium Tetrafluoroborate. Aniline or substituted aniline (10 mmol) was dissolved in distilled water

(4 mL) and 3.4 mL of 50% hydrofluoroboric acid was added. The reaction mixture was cooled to $0^\circ C$ using an ice bath, and sodium nitrite solution (690 mg in 1.5 mL) was added dropwise.⁶ Then, the solution was stirred for 40 min at $0-5^\circ C$ and the resulting precipitate was collected by filtration and redissolved in a minimum amount of acetone. After that, diethyl ether was added and diazonium tetrafluoroborate was precipitated. Diazonium salt was washed several times with diethyl ether and dried under a vacuum.

Arylation of Substituted Naphthoquinone. 1,4-SNQ [0.58 mmol, 1 equivalent weight (equiv wt)] and diazonium salt (1.161 mmol, 2 equiv wt) and 7.5 mol % of the disodium salt of EY were dissolved in 5 mL of DMSO in an oven-dried photovoltaic cell. Then, the reaction mixture was sonicated for 3–5 min to dissolve the diazonium salt properly. After that, the vial was kept inside the photoreactor under stirring for 8 h at RT. TLC monitored the progress of the reaction. After 8 h, the reaction was quenched with saturated $NaHCO_3$ solution (250 mL) and extracted with chloroform (3×100 mL). The combined organic layer was dried with anhydrous Na_2SO_4 . The organic layer was evaporated under reduced pressure. The crude residue was purified by column chromatography (200–300 mesh silica) with a mixture eluent of hexane/ethyl acetate (9:2 v/v) (70–90% yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c04289>.

Kinetics and steady-state quenching data, HRMS spectra, NMR spectra, electronic and steric effect of the substituents of naphthoquinones, and arylation of 1,4-benzoquinone (PDF)

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Notes

The authors declare no competing financial interest.

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