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On-water accelerated sulfenylation of indole derivatives under visible light irradiation†

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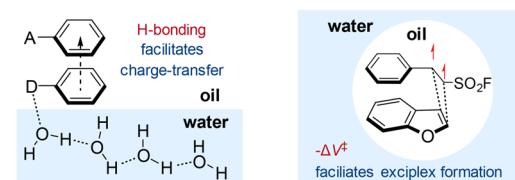
A visible-light promoted sulfenylation of *N*-carboxyindoles with thiols showed substantially higher rate and selectivity when conducted “on water”. An EDA complex was proposed to form at the water–oil interface, generating thiyl radicals and thus initiating a chain reaction.

Organic chemists have avoided water as the reaction medium, perhaps due to the preconception that substrate dissolution is necessary for reactivity. Consequently, development of organic reactions in pure water has been less common.¹ This notion was challenged in 1980 when Rideout and Breslow observed a significant increase in the rate and the selectivity of Diels–Alder reactions in pure water due to the hydrophobic effect.² In 2005, Sharpless and coworkers demonstrated that the rate of certain pericyclic reactions and epoxide openings in water was faster than in an organic phase.³ For this rate enhancement, reactant heterogeneity is essential, with organic reactants typically forming liquid droplets, assisted by melting point depression.⁴ This dramatic acceleration in the form of an aqueous suspension was termed an “on-water” reaction.

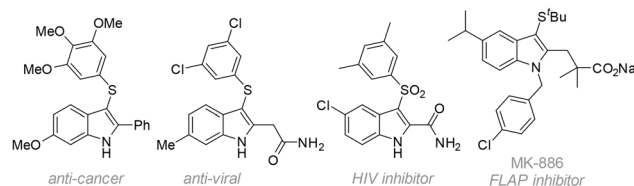
In connection with green chemistry,⁵ the application of aqueous medium in visible-light photochemical reactions has recently received increasing attention.⁶ Potential advantages such as enhanced reductive power of the photocatalysts,⁷ lowered LUMO of the substrates,⁸ and facilitated proton transfer⁹ have stimulated increased interest in exploring the aqueous phase for photocatalytic applications. However, photochemical reactions of water-insoluble substrates that exhibit significant acceleration on water remain limited.¹⁰ Recently, the König group reported that cross coupling of

cyano heteroarenes can be accelerated in a eutectic mixture of organic reactants, where interfacial hydrogen bonding at the water–oil interface facilitates the formation of a hydrophobic electron donor–acceptor (EDA) complex (Scheme 1A, left).^{10a} The Bae group reported that a (2 + 2) cycloaddition of β -aryl ethenesulfonylfluorides and benzofurans, unreactive in any other organic solvents, uniquely proceeded in water, with the rate surpassing neat conditions.^{10b} Here, on-water acceleration was ascribed to the hydrophobic effect favoring negative volume of activation (ΔV^\ddagger) to effectively capture the triplet enthenesulfonyl fluoride with benzofuran (Scheme 1A, right).

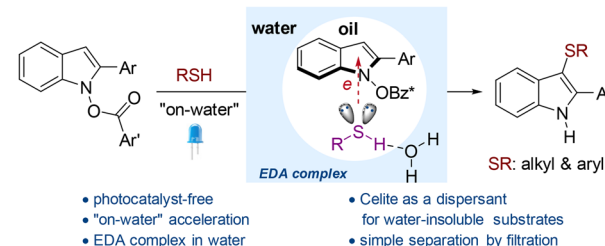
A. On water-accelerated photocatalysis



B. Biological activity of sulfenylated indoles



C. Sulfenylation of *N*-carboxyindole: *This report*



Scheme 1 Visible-light-promoted on-water catalysis: sulfenylation of *N*-carboxyindoles.

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Recently, we^{11,21,22} and others¹² have developed substitutions of *N*-carboxyindoles as unpoled indole precursors under Brønsted/Lewis acid, Cu, and photocatalytic conditions. Given the biological importance of 3-sulfonylindoles (Scheme 1B),¹³ substantial efforts have been made *via* S_EAr reactions of indoles with various electrophilic sulfonylating reagents.¹⁴ In contrast with previous approaches, we present herein a redox-neutral sulfonylation with thiols using *N*-carboxyindoles as unpoled indoles. In the pursuit of environmentally sustainable conditions, we discovered that the substitution occurs in water with significantly higher rate and selectivity compared to organic solvents (Scheme 1C). Our findings align with the concept of “on-water” accelerated photocatalysis.

Initially, we noted that previous sulfonylation methods¹⁴ had lower yields and a narrower scope for forming alkyl thioethers compared to aryl thioethers. Consequently, our primary optimization goal was to investigate the sulfonylation of *N*-carboxyindole **1a** using aliphatic thiol **2a** (Table 1). We first tested photocatalysts in acetonitrile under blue LEDs irradiation (450 nm) (Table S1†). Use of Ru(bpz)₃(PF₆)₂ resulted in extensive decomposition of product **3aa** (entry 1), which indicated the photoirradiation-induced instability of **3aa** is a significant challenge for optimization. Without a photocatalyst, the reaction was somewhat cleaner, but had low conversion (entry 2). The rate and selectivity were found to be highly solvent-dependent (Table S2†). In ether, the product decomposition was significantly diminished (entry 3). The reaction in an aqueous suspension of **1a** resulted in the cleanest conversion (LCMS in Fig. S1†), albeit incomplete (entry 4). The low conversion was due to the insolubility of **1a** in water. For example, a mixture of **1a** and **2a** (4 equiv.) in water forms a heterogeneous mixture at RT (Fig. 1A).¹⁵ During the reaction, an orange gummy deposits sat on the magnetic stir bar, encapsulating the unreacted **1a** (Fig. 1B). Attempts to improve solu-

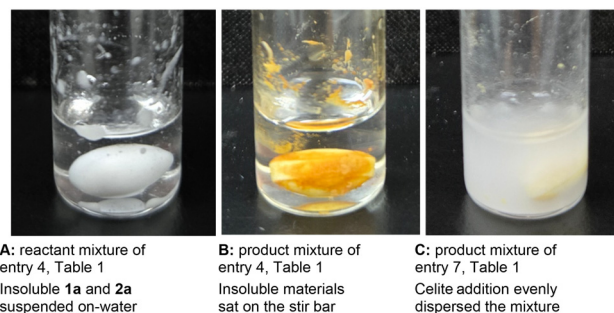


Fig. 1 The effect of Celite as dispersant.

bility using a co-solvent (entry 5) or a surfactant (entry 6) resulted in higher conversion, but were accompanied by significant decomposition. Interestingly, the addition of Celite led to complete conversion, yielding **3aa** in 83% yield (entry 7). It was assumed that Celite mechanically disrupts solid aggregates, resulting in an even dispersion of reactants. This accelerates full conversion and minimizes over-irradiation-induced decomposition (Fig. 1C). The effect of Celite was not distinct in other solvents, including EtOH, ACN, and ether and Celite was more effective as a dispersant than silica or MS 4 Å (Table S2†). Using shorter or longer wavelength LEDs resulted in a poorer mass balance due to extensive photo-induced decomposition or inactivity, respectively (entries 8 and 9). Testing different leaving groups in **1a** revealed that *p*-CF₃ benzoate provided the best yield (Table S3†).

With the optimized conditions established, we examined sulfonylation reaction of **1a** starting with aliphatic thiols (Scheme 2). Primary, secondary, and tertiary thiols underwent smooth sulfonylation without issues (entries 1–6). Diverse functional groups, including a silane, an ester, a thiol, and a Boc-protected amine (entries 7–10) were compatible. For less reactive thiols, extended irradiation (entries 7–10) and/or a larger amount of thiol (entries 9 and 10) was required. Notably, *N*-protected cysteine underwent efficient sulfonylation (entry 11).

The conditions developed for aliphatic thiols were directly applied to aromatic thiols (entries 12–27). The sulfonylation proceeded smoothly regardless of the *o*-, *m*-, and *p*-substituents of the aryl thiols (entries 12–23). A furyl thiol gave **5an** smoothly (entry 24), but thiazolyl, pyridyl, and pyrimidyl thiols produced unknown byproducts under standard conditions: change of solvent and wavelength of light (CH₃CN, 405 nm) produced reasonable yields of **5am**–**5ap** in these cases (entries 25–27). Notably, the synthesis of **5aa** can be conducted on a 1 mmol scale, yielding nearly the same high yield (94%), demonstrating the robustness of the current protocol.

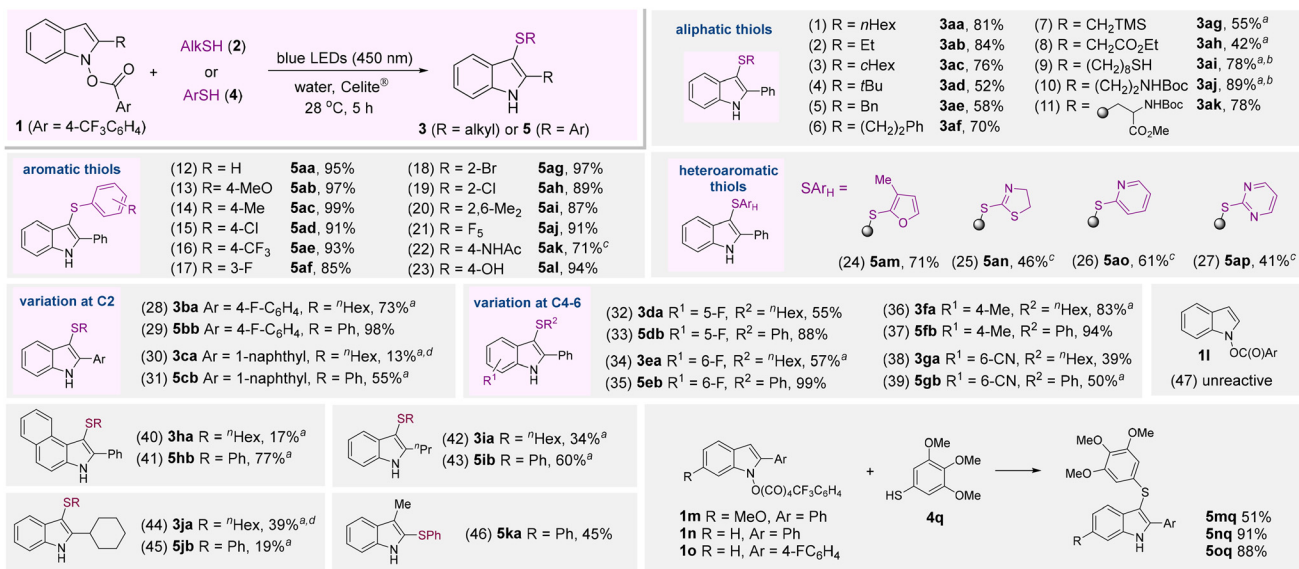
Then we tested differently substituted indoles **1** for sulfonylation with both *n*HexSH and PhSH (entries 28–47). Substrates with a different aryl group at C2 (entries 28–31) and substitutions at C4, C5, C6 positions of the indole core (entries 32–39) were broadly successful. Nonetheless, sterically demanding substrates, such as **1c** and **1h** proved challenging (entries 30–31 and 40–41), especially in reaction with an ali-

Table 1 Reaction conditions development^a

Entry	Solvent	Additive ^b	Conv. (%)	3aa (%)	A (%)
1	ACN	[Ru] ^c	75	39	6
2	ACN	None	58	33	10
3	Ether	None	86	66	10
4	H ₂ O	None	59	48	8
5	H ₂ O/ACN (1/1)	None	78	57	16
6	H ₂ O	CTAB ^d	86	14	9
7	H ₂ O	Celite	>99	83	15
8 ^e	H ₂ O	Celite	>99	63	26
9 ^f	H ₂ O	Celite	0	—	—

^a A mixture of **1a** (0.05 mmol), *n*HexSH (**2a**, 0.2 mmol) and solvents (1 mL) were placed in a vial and was capped under air; crude yields based on ¹H NMR spectra. ^b 50 mg of additives were added. ^c Ru(bpz)₃(PF₆)₂ (5 mol%). ^d Cetyltrimethyl ammonium bromide (1.5 equiv.). ^e λ = 405 nm. ^f λ = 515 nm.





Scheme 2 Sulfenylation with alkyl (**2**) and aryl (**4**) thiols. Reaction conditions: **1** (0.1 mmol), RSH (0.4 mmol), and Celite (100 mg) in water (2 mL) was irradiated with blue LEDs (450 nm, 18 W) for 3–5 h; isolated yields after SiO₂ chromatography. ^a Reaction time: 17 h. ^b Alkyl thiol (6 equiv.). ^c Difference from the standard conditions: solvent (CH₃CN) and wavelength (405 nm). ^d The yield of **3ca** and **3ja** was determined from the crude ¹H NMR spectra.

phatic thiol **2a**. Similarly, indoles with alkyl groups at the C2, gave low conversion (entries 42–45). Interestingly, 3-methylindole **1k** provided C2-sulfenyl product **5ka** in 45% yield (entry 46). However, unsubstituted *N*-carboxyindole **1l** was unreactive under the standard conditions (entry 47). To our delight, the current protocol can be applied to the synthesis of biologically active tubulin polymerase inhibitors **5mq–5oq** (Scheme 2).^{13,16}

Subsequently, we investigated the reaction mechanisms. In the presence of TEMPO (2 equiv.), the formation of both **3aa** or **5aa** was completely suppressed (Fig. S4†). In the reaction with PhSH, PhS-OTMP (*m/z* = 266.1572 for [M + H]⁺) was identified, indicating a crucial role of the thiyl radical. We further examined the effects of light (Table S5†). With LEDs off, the reaction of **1a** with *n*HexSH **2a** or PhSH **4a** did not proceed efficiently, suggesting that a thiyl radical is predominantly formed through photochemical means.¹⁷

The distribution of reactants can be monitored by ¹H NMR spectroscopy on a heterogeneous mixture of **1a** and **2a** in water (Fig. 2A and Fig. S9–S12†).^{10a} For instance, ¹H NMR spectrum of a immediately agitated mixture of **1a** (formal molarity, 0.01 M) and *n*HexSH (**2a**, 4 equiv.) in D₂O revealed a small amount of **1a** and a large quantity of **2a** in oil droplets, with a minute quantity of **2a** solvated in water (Fig. 2A, up). When filtered through a syringe filter, the oil droplets were removed, leaving only the aqueous solution of **2a** in the D₂O phase (Fig. 2A, down). Notably, none of **1a** remained in the aqueous phase, suggesting that **1a** primarily located within the oil droplets alongside the majority of **2a**. In addition, it was found that the reaction required a stirring speed of over 300 rpm (Table S4†) to presumably provide sufficient interface between the water and oil droplets.

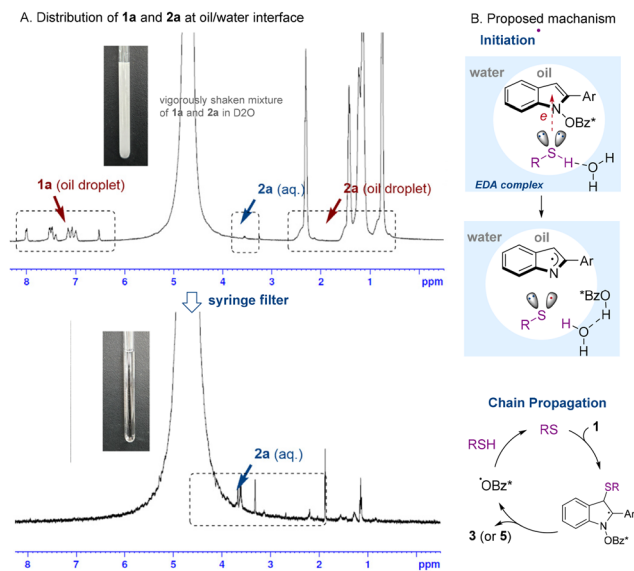


Fig. 2 Mechanistic experiments and a proposed mechanism.

UV-Vis spectroscopy revealed the interaction of **1a** with **2a** at the water/oil interface (Fig. S7 and S8†). Addition of **2a** into a solution of **1a** in CH₃CN did not cause any spectral change, but increasing the water ratio in the solvent mixture led to a progressively larger bathochromic shift. This suggests the formation of an electron donor–acceptor (EDA) complex at the water–oil interface.^{10a} The quantum yield was measured to be $\Phi > 54$ for the reaction of **1a** with **4a** (section 4.6, ESI†), supporting presence of a radical chain.



Based on the above experiments, a plausible mechanism was proposed as shown in Fig. 2B. Visible light absorption of the EDA complex between **1** and **2** (or **4**) at the oil–water interface may facilitate a single electron transfer (SET)¹⁸ accompanied by a proton transfer (PT).^{4c} Thus generated thiyl radical adds to **1**, followed by N–O bond homolysis to form **3** (or **5**) and a carboxylate radical. Alternatively, the radical displacement ($S_{RN}2'$) may be followed,¹⁹ in which C–S bond formation and N–O bond cleavage are concerted. The liberated carboxy radical regenerates the thiyl radical through hydrogen atom transfer (HAT). This radical chain appears to be short-lived, as indicated by light on–off experiments conducted with **1a** and PhSH in CH₃CN (Fig. S5†). In the reaction with aromatic thiols, the mechanism slightly differs: a mixture of **1a** and PhSH exhibits a bathochromic shift even in CH₃CN, suggesting EDA formation through π – π stacking interaction.²⁰ Similarly to above, this bathochromic shift is further enhanced with increased water composition (Fig. S8†).

One of the practical advantages of aqueous reaction is ability to isolate the product without extractive workup. Exploiting this advantage is demonstrated in the C–S coupling and oxidation into sulfoxide: the crude mixture of **5aa** was filtered, washed with a solvent of the next reaction (CH₂Cl₂) and the filtrate was treated with *m*CPBA (Fig. S2, section 3.2.2, ESI†). In this fashion, synthesis of sulfoxide **6aa** telescoped in good yield (91%) without involving extractive workup of the intermediate **5aa**.

In summary, we developed a redox-neutral sulfenylation of unpoled indole derivatives for the synthesis of 3-sulfenylindole. When irradiated with blue LEDs, the sulfenylation occurred in the absence of photocatalyst and the reaction was significantly accelerated by making the reaction mixture heterogeneous in an “on-water” mode. The reaction may proceed through the formation of an EDA complex at the water–oil interface, facilitating the formation of a thiyl radical as a radical chain carrier. For on-water reactions of water-insoluble substrates, Celite was found to be effective as a dispersant to ensure even conversion and to prevent photo-induced decomposition of products.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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