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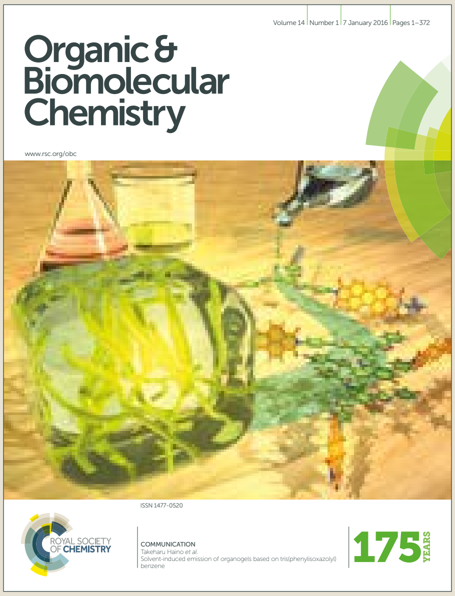
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Eosin Y Photoredox Catalyzed Net Redox Neutral Reaction for Regiospecific Annulation to 3-Sulphonylindoles via Anion Oxidation of Sodium Sulfinate Salts

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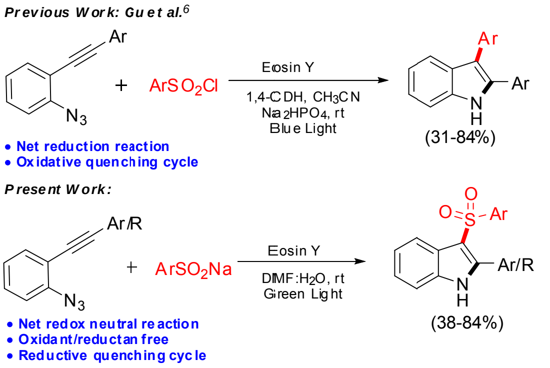
Rajendra S. Rohokale[a,b] Shrikant D. Tambe[b] and Umesh A. Kshirsagar[*b]

Eosin Y photoredox catalyzed net redox neutral process for 3-sulfonylindoles via the anionic oxidation of sodium sulfinate salts and its radical cascade cyclization with 2-alkynyl-azidoarenes was developed with visible light as a mediator. The reaction offers metal and oxidant/reductant free, visible light mediated vicinal sulfonamination of alkynes to 2-aryl/alkyl-3-sulfonylindoles and proceeds via generation of sulfur-centered radical through direct oxidation of sulfinate anion by excited photocatalyst with reductive quenching cycle. Mild conditions, organic dye as photo-catalyst, bench stable and easily accessible starting materials make the present approach green and attractive.

Visible light-mediated photo-redox catalysis has emerged as an alternative, green, economical and practical approach for generating reactive radicals/intermediates in a catalytic manner over the past decade.[1] Chemical and electrochemical oxidation methods have some limitations such as formation of by-products, need of a specially designed set-up and suffers from cost-effectiveness.[2] Consequently, visible light photo-redox catalysis has re-invoked great attention from the synthetic community, not only as an alternative for photochemical and electro-chemical reactions but also for classical synthetic methods.[1] Metal-based[3] photo-redox catalysts and organic dye-based[4] photo-redox catalysts have proven immensely useful for various bond-forming reactions. In particular, non-toxic, cost-effective organic dyes are of growing interest, and offer advantages in comparison to metal-based photo-catalysts.

Photoredox catalyzed reactions are generally categorized in two major mechanistic paths in which quenching of excited photo catalysts is facilitated by either (a) 'oxidative quenching cycle' with the transfer of an electron to the substrate or the oxidant, or (b) 'reductive quenching cycle' with the acceptance of an electron from substrate or reductant.[1] Nicewicz[1d] further classified the general redox outcomes of these photo-catalyzed reactions as (i) net oxidative reactions, which require an external electron acceptor (oxidant), (ii) net reductive reactions, which require an external electron donor (reductant), and (iii) net redox-neutral reactions.

A single-electron oxidation of anions is one of the potential concepts to generate reactive heteroatom-centered radicals, due to the bench stability, easy availability and handling of inorganic anion salts and their further applications in organic synthesis such as bond-forming and oxidation reactions.[2,5] Despite this, the reports on visible light-induced anion oxidation generating reactive radical intermediates or their utilization for further synthesis are rather scarce.[2] Recently, Gu *et al.*, reported the visible light initiated Eosin Y photo-catalyzed net reduction reaction for the synthesis of unsymmetrical 2,3-diarylsubstituted indoles from 2-alkynyl-azidoarenes and sulfonyl chlorides in the presence of base and 1,4-cyclohexadiene (1,4-CHD) as a hydrogen radical donor, which involved an oxidative quenching cycle (Scheme 1).[6] This reaction proceeds by generation of an aryl radical via desulfynative pathway of sulfonyl chloride through photo-catalysis and subsequent annulation. Herein, we report our outcomes on visible light photoredox catalysis anion oxidation of sodium sulfinate salts in the presence of 2-alkynyl-azidoarenes for vicinal sulfonamination of alkynes to construct 2-aryl/alkyl-3-sulfonylindole derivatives via net redox neutral



Scheme 1 Photoredox catalyzed reactions of 2-alkynyl-azidoarenes

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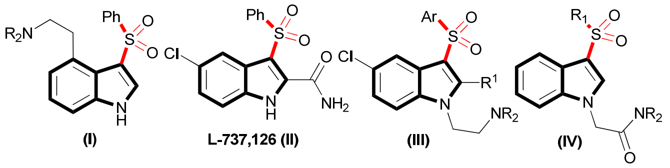


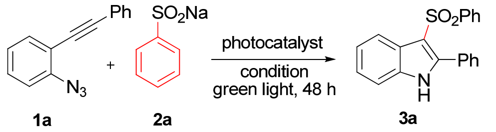
Figure 1: Biologically active sulfonylindole derivatives.

reaction, which involved the reductive quenching cycle with the preserved sulfonyl unit.

Sulfonylated molecules[7] in general and 3-sulfonyl-indole[8] derivatives in particular have been a focus of attention due to their crucial role in the medicinal and pharmaceutical fields owing to their remarkable biological activities[9] such as norepinephrine reuptake inhibitor (**I**), HIV-1 non-nucleoside reverse transcriptase inhibitor (**II**), 5-HT_6 receptor (**III**) and orexin receptor antagonist (**IV**) (Figure 1). Hence sulfonylation reactions and the synthesis of sulfonylated heterocycles has received great attention.[7,8] Recently, *tert*-Butylhydroperoxide (TBHP) mediated vicinal sulfonamination of alkynes was reported for 3-sulfonylindoles at elevated temperature.[8a]

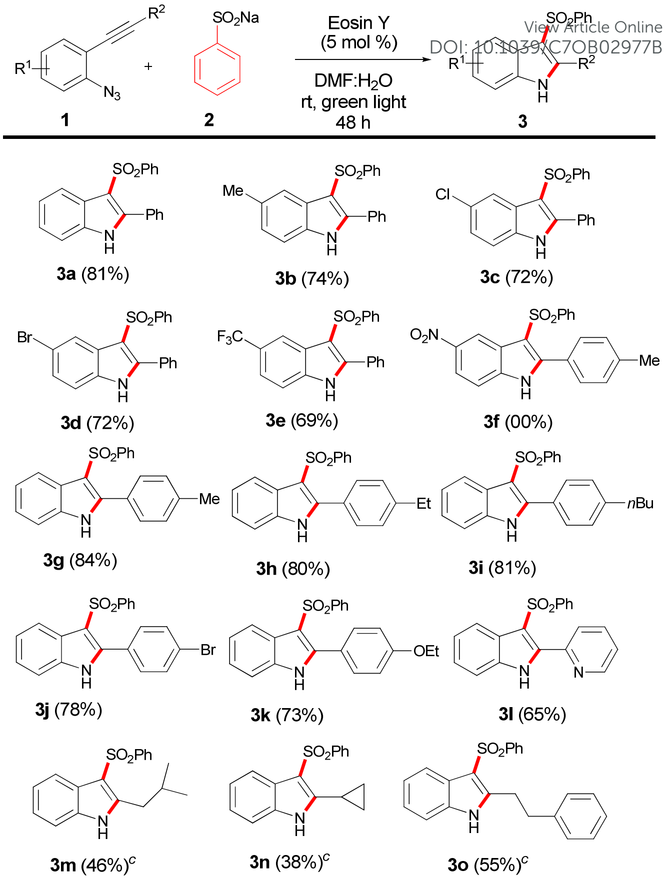
For optimization of the reactions in the present work, initially, the reaction between 1-azido-2-(phenylethynyl)benzene **1a**[10] and phenyl sodium sulfinate salt **2a** was conducted in dichloromethane (DCM) at room temperature in the presence of 5 mol % Eosin Y as photocatalysts (entry 1, Table 1). Formation of product **3a** was observed in low yield (28%). This positive result encouraged us to carry out the further optimization of reaction conditions. The reaction was examined by changing the solvents (entries 1-7) in which a combination of DMF/H_2O (9:1) was found to be the best solvents to afford the highest yield (81% entry 7).[11] The screening by different photocatalysts, for example, Na_2-Eosin Y, Rose Bengal, $Ru(bpy)_3Cl_2$ and $Ir(ppy)_3$ (entries 8-11) did not improve the yield of **3a**. It has been realized that both photoredox catalysts (entries 12) and visible light (entries 13) are necessary for the reaction to occur. With the optimized reaction conditions, the substrate scope and limitations of 2-alkynyl-azidoarenes were examined (Scheme 2).[11] Various 2-alkynyl-azidoarenes were prepared and reacted with phenyl sodium sulfinate salt (**2a**). The reaction was successfully amenable to a wide range of 2-phenylethynyl aryl azides (**1a-e**), affording the desired 3-sulfonylindoles 3a-e in 69-81% yields. When 1-azido-4-nitro-2-(phenylethynyl)benzene (**1f**) reacted under the same condition, the corresponding product **3f** was not formed. Next, azido benzenes with both aryl alkynyl and alkyl alkynyl were further investigated. A variety of azidobenzenes with arylethynyl i.e., *p*-Me, *p*-Et, *p*-nBu, *p*-Br, *p*-OEt proceeded well in the reaction, giving rise to the corresponding products **3g-k** in 73-84% yields. The azidobenzene with 2-pyridinyl ethynyl delivered the respective product **3i** (65% yield). When azidobenzenes with different aliphatic alkynyls such as 4-methylpent-1-yne, ethynylcyclopropane as well as but-3-yn-1-ylbenzene were treated with sodium phenyl sulfinate, the corresponding products **3m-o** were formed in moderate yields (46, 38 and 55%, respectively). Further to explore the scope of sodium sulfinate salts, a variety of sodium sulfinate salts were applied under the optimised reaction condition with 1-azido-2-(phenylethynyl)benzene **1a** (Scheme 3). Aryl sodium sulfinate salts such as *p*-Me, *p*-F, *p*-Br, *p*-Cl and naphthalene-2-sulfinate

Table 1 Optimization Studies[a,b]



entry	photo-catalyst	solvents	yield (%)[b]
1	Eosin Y	DCM	28
2	Eosin Y	$PhCF_3$	NR
3	Eosin Y	CH_3OH	NR
4	Eosin Y	THF	44
5	Eosin Y	HFIP	20
6	Eosin Y	DMSO	25
7	Eosin Y	DMF:H_2O	81
8	Na_2-Eosin Y	DMF:H_2O	60
9	Rose Bengal	DMF:H_2O	trace
10	$Ru(bpy)_3Cl_2$	DMF:H_2O	trace
11	$Ir(ppy)_3$	DMF:H_2O	trace
12[c]	none	DMF:H_2O	NR
13[d]	Eosin Y	DMF:H_2O	NR

[a]Reaction conditions: **1a** (0.04 mmol), **2a** (0.12 mmol), photo-catalyst (5 mol %), solvent (1 mL) and stirring for 48 h under nitrogen atmosphere. [b]Isolated yield. [c]No photo catalyst. [d]No light



Scheme 2 Scope of 2-Alkynyl Arylazides.[a,b] [a]Reaction condition: 0.14 mmol **1a**, 0.41 mmol **2**, 5 mol % Eosin Y, DMF/H_2O (9:1, 1.5 mL), rt, 48 h; [b]Isolated yields are given. [c]Reaction was performed using THF/H_2O (9:1) as solvent.

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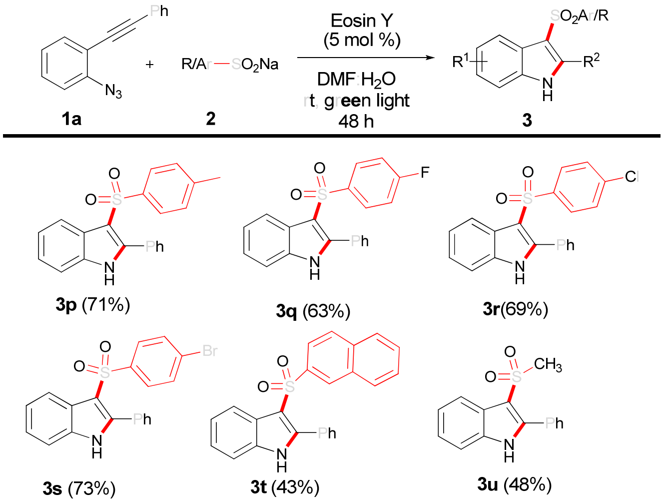
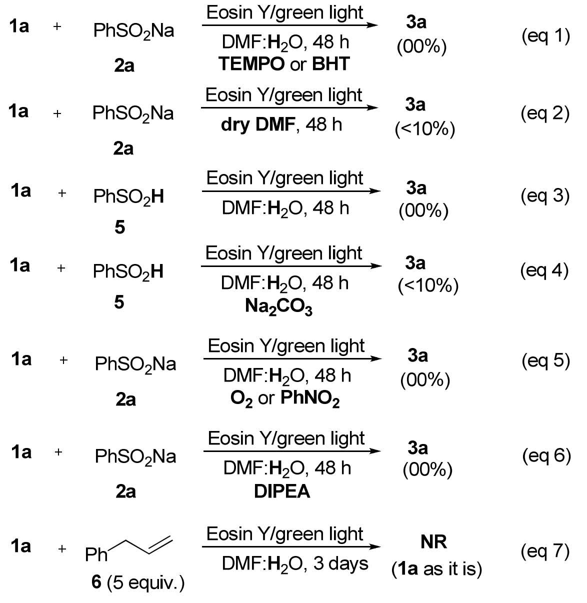


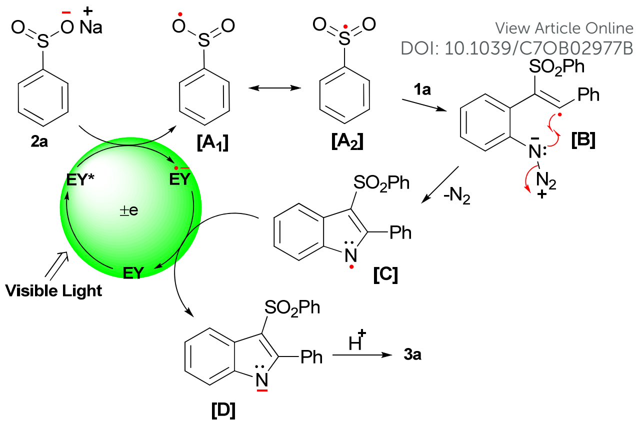
Scheme 3 Scope of sodium sulfinate salts.[a] [a]Reaction conditions: 0.14 mmol **1a**, 0.41 mmol **2**, 5 mol % Eosin Y, DMF/H$_2$O (9:1, 1.5 mL), rt, 48 h.

proceeded smoothly to deliver the products **3p-t** in 43-73% yields. Interestingly, the methyl sulfinate salts afforded the targeted products **3u** in 48% yield.

To have mechanistic insight accompanying the presented reaction, some control experiments were carried out. When the reaction was performed under the standard condition in the presence of classical radical inhibitors such as BHT and TEMPO, the formation of product was not observed (Scheme 4, eq 1). The absence of water led to the product with its yield <10% (eq 2). To analyze the role of anion of sulfinate, the reaction was carried out using the phenylsulfinic acid instead of sulfinate salt; the product **3a** was not obtained (eq 3). Surprisingly, in the presence of Na$_2$CO$_3$, the desired product was obtained with <10% yield (eq 4). When the reaction was performed in the presence of an external oxidant such as oxygen or nitrobenzene (eq 5), and the DIPEA as an external reductant (eq 6) reaction failed to give **3a**. To check the formation of nitrene from azide by photocatalysis,[12] reaction was carried out with allyl benzene instead of sodium sulfinate salt (eq 7). No reaction was observed and **1a** was recovered which rule out the possibility of formation of nitrene.



Scheme 4 Control experiment



Scheme 5 A plausible mechanism pathway

The present reaction, the above control experiments, and the literature[1d,2,5] suggest that the reaction follows a reductive quenching cycle in net redox neutral pathway. A plausible radical cascade reaction pathway has thus been proposed (Scheme 5). Visible light induced photo-excitation of Eosin Y (**EY**) generates excited state of Eosin Y (**EY***). Direct one electron oxidation of the sulfinate anion by this ambivalent reactive excited state **EY*** provides S-centered sulfonyl radical (**A$_2$**) with reduction of **EY*** to **EY•-**.[13] Regioselective addition of the sulfonyl radical on the triple bond gives olefinic radical intermediate **B**. Intramolecular radical cyclization of **B** with the azide nitrogen provides *N*-centered radical intermediate **C** upon N$_2$ release. Oxidation of **EY•-** to the ground state **EY** by electron transfer to radical intermediate **C** may provide intermediate **D**, which on proton abstraction from the reaction mixture led to **3a**.

In conclusion, we disclosed visible light induced, Eosin Y photo-redox catalyzed net redox neutral reaction by direct oxidation of sulfinate anion through a reductive quenching cycle for a radical cascade cyclization of 2-alkynyl-azidoarenes to produce 2-aryl/alkyl-3-sulfonyl-indoles. To our knowledge, this is the first visible light induced Eosin Y photo-redox catalyzed vicinal sulfonamination of alkynes. Mild conditions such as room temperature, visible light as a traceless energy source, metal free, oxidant/reductant free, stable and easily accessible starting materials are further highlights. The potential of anion oxidation for the construction of a variety heterocyclic compounds and natural products of biological importance and details on the mechanistic aspects are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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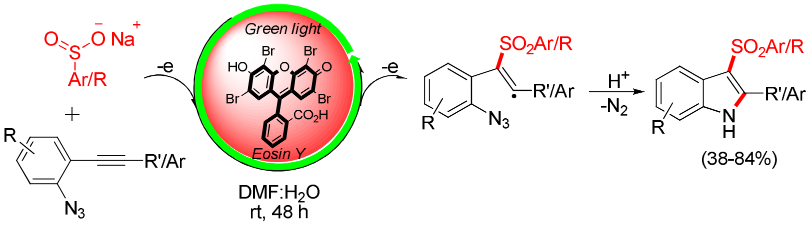

- **Net redox neutral Reaction**
- **Anion oxidation**
- **Reductive quenching cycle**
- **Oxidant/reductant free**
- **Photo-redox catalysis (organic dye)**
- **Mild reaction condition**