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Organocatalytic visible light mediated synthesis of aryl sulfides†

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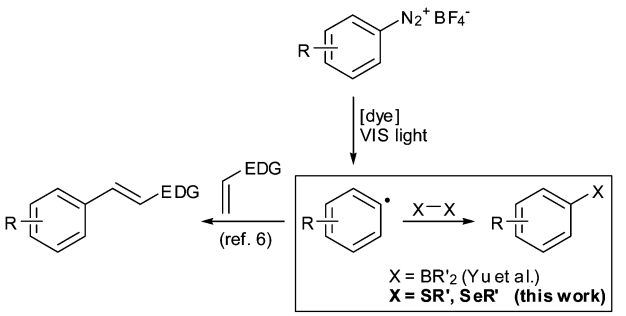
Photo-sensitized synthesis of arylsulfides from arenediazonium salts in the presence of eosin Y has been developed. This protocol exhibits high functional group tolerance and a wide substrate scope and is an attractive alternative to the thermal reaction that involves explosive intermediates.

The development of mild and sustainable protocols for aromatic substitutions is of utmost importance to the synthesis of fine chemicals, agrochemicals, pharmaceuticals, materials, and natural products.[1] Numerous thermal, Lewis acid-mediated, and metal-catalyzed protocols are currently available to the organic chemist in order to access a large variety of substitution patterns. The re-discovery of visible light as an abundant energy source for the activation of chemical reactants has prompted renewed interest in light-mediated aromatic substitutions as a powerful alternative to metal-catalyzed "dark" reactions.[2] Such catalytic reactions in the presence of suitable photo-sensitizers mostly involve single electron transfer (SET) processes that bear a close conceptual relationship with Sandmeyer-type reactions.[3] The merit of the photo-catalytic synthesis is the mild generation of aryl radicals by photo-sensitized electron transfer which avoids the direct photolysis of bonds requiring UV light[4] and the employment of stoichiometric copper(I) salts.

Early studies of photoredox catalysis utilized arene-diazonium salts as precursors for aryl radicals, whose choice is not deliberate: diazonium salts are easily prepared and undergo facile and irreversible oxidation due to the release of dinitrogen. $Ru(bpy)_3Cl_2$-sensitized intramolecular Pschorr-type arylations were first reported by Deronzier in 1984.[5] Modern developments include intermolecular arylations of electron-rich π-donors for the synthesis of biaryls, stilbenes, α-arylketones, and thiophenes (Scheme 1).[6] However, the prevalent use of ruthenium and iridium photo-catalysts is still a severe limitation of many photo-redox protocols in terms of sustainability and scalability. The persistent quest to introduce cheaper metal-free dyes has been addressed with the successful use of eosin dyes.[7] While these reports clearly demonstrate the viability of aryl radical trapping by π-donors (*i.e.* alkenes, arenes), examples utilizing σ-donors have remained scarce. To the best of our knowledge, there is only one report where diboranes have been oxidatively cleaved to give arylboronates (Scheme 1).[8] In an effort to extend this general concept to the synthesis of thioethers, we have developed visible light-mediated thiolation of diazonium salts in the presence of eosin Y. Arylsulfides are key structural motifs in synthetic and natural molecules.[9] Their synthesis is usually performed by treatment of readily available arenediazonium salts with thiols under neutral or basic conditions.[10] However, the intermediate diazosulfide species is a potent explosive even under wet conditions and has already caused violent detonations in many instances.[11]



Scheme 1 Formal nucleophilic substitutions at arenediazonium salts *via* visible light mediated SET reductions.

We envisioned the oxidative cleavage of disulfides by aryl radicals to be a promising catalytic strategy for the synthesis of aryl sulfides.[11,12] The high nucleophilicity of sulfur should entail rapid trapping of the radical and avoid the accumulation of potentially hazardous intermediates, while the neighboring sulphur atom can stabilize partial unsaturation or charges. In combination with the mild visible light-mediated generation of

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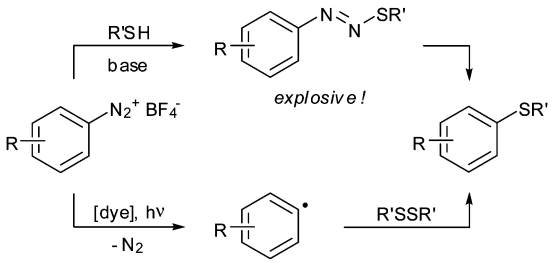
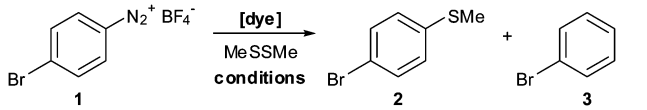


Scheme 2 Azo coupling *vs.* a disulfide route to aromatic sulfides.

Table 1 Selected optimization experiments[a]



Entry	Solvent	Dye (mol%)	Equiv. DMDS	2/3 [%]
1[b]	DMSO	Eosin Y (5)	5	49/—
2	DMSO	Eosin Y (5)	5	73/—
3[c]	DMSO	Eosin Y (5)	5	71/—
4	NMP	Eosin Y (5)	5	29/—
5[d]	MeCN	Eosin Y (5)	5	65/—
6	DMF	Eosin Y (5)	5	25/27
7[e]	DMF	Eosin Y (5)	—	—/81
8	DMSO	Fluorescein (5)	5	25/—
9	DMSO	Neutral red (5)	5	29/—
10	DMSO	$Ru(bpy)_3Cl_2$ (5)	5	69/—
11	DMSO	Eosin Y (2)	5	72/—
12	DMSO	Eosin Y (1)	5	63/—
13	**DMSO**	**Eosin Y (2)**	**1.5**	**73/—**
14	DMSO	Eosin Y (2)	1	42/—
15[g]	DMSO	—	1.5	—/—
16	DMSO	—	0.5	3/—
17[g]	DMSO	Eosin Y (2)	0.5	3/—

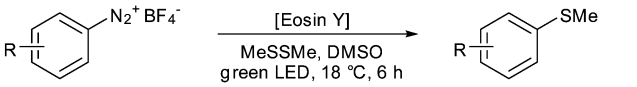
[a] Standard conditions: 0.5 mmol 4-bromobenzenediazonium tetrafluoroborate, 0.025 mmol eosin Y, 2.5 mmol dimethyldisulfide (DMDS), 2 mL solvent, 18 °C, 6 h irradiation with green LED (λ = 525 nm, 3.8 W). [b] 2 h. [c] 20 h. [d] 7 mL MeCN. [e] No DMDS. [f] Without eosin Y. [g] In the dark.

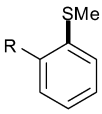
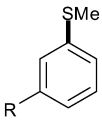
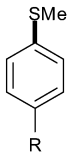
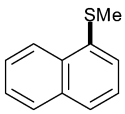
aryl radicals from arenediazonium salts, this would provide an attractive alternative to thermal reactions involving explosive intermediates (Scheme 2). The presence of free aryl radicals in the related "dark" process with stoichiometric copper salts was proven using EPR spectroscopy.[13]

Initial experiments with 4-bromobenzenediazonium tetrafluoroborate (**1**) and dimethyldisulfide (dmds), a commercial food additive and a sulfiding agent, supported our assumption (Table 1). The optimized set of conditions includes irradiation (green LED, λ_{max} = 525 nm, 3.8 W) of a solution of **1**, 1.5 equiv. dmds, and eosin Y (2 mol%) in dimethylsulfoxide (DMSO) at 18 °C for 6 h. *N*-Methyl pyrrolidinone (NMP) showed low solubilization of **1**, while *N*,*N*-dimethylformamide also effected reductive dediazotation.[14] Fluorescein, Neutral Red, and $Ru(bpy)_3Cl_2$ gave lower yields.

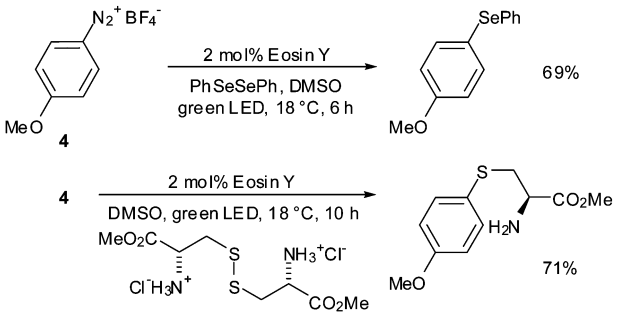
A catalyst-free dark reaction gave no product. When irradiating this mixture, very low yields were observed possibly due to a charge transfer complex between **1** and DMSO which exhibits absorbance in the visible region.[15] The scope of the protocol was evaluated by employment of various arenediazonium salts (Table 2). The reaction conditions tolerated the presence of esters, nitro groups, and halides (F, Cl, Br), while concomitant

Table 2 Substrate scope



Entry	R	Aryl methyl sulfide	Yield [%]
1	2-Me		80
2	2-CO_2Me		77
3	2-CF_3		68
4	2-NO_2		48
5	3-Cl		89
6	3-NO_2		60
7	4-OH		57
8	4-OMe		87
9	4-Me		77
10	4-Cl		85
11	4-Br		73
12	4-I		51[a]
13	4-F		69
14	4-CF_3		67
15	4-NO_2		39
16	–C_4H_4–		31[b]

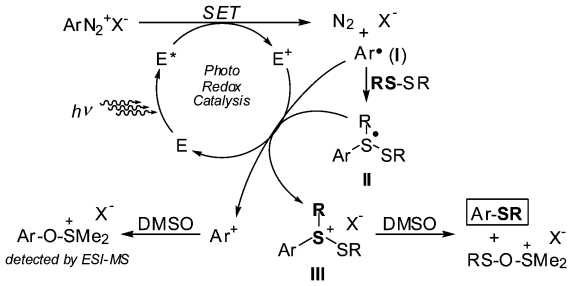
[a] Polymer formation observed. [b] 12% 1,4-di(methylsulfanyl)naphthalene.



Scheme 3 Synthesis of cysteine and selenide derivatives.

substitution of iodide and resultant polymer formation were observed (entry 12). Iodoarene moieties are subject to iodine transfer to aryl radicals.[16] Consistently, addition of iodobenzene to the reaction of 4-iodobenzenediazonium tetrafluoroborate also afforded 1,4-diiodobenzene. Conversion of 1-naphthalenediazonium salt was unselective giving a mixture of mono- and disubstituted products (entry 16). Similar selectivity was observed in the presence of diphenyldiselenide to give an unsymmetrical diarylselenide (Scheme 3).[17] The synthesis of an arylsulfide bioconjugate bearing an amino acid residue was realized by reaction with dimethyl L-cystinate.[18]

On the basis of previous reports,[5,6] we propose a mechanism for the photocatalytic thiolation (Scheme 4). The arene-diazonium salt (**I**) is susceptible to SET reduction by the excited photocatalyst. The resulting aryl radical **II** is attacked by the nucleophilic disulfide to give a trivalent sulfur radical, **III**, which is stabilized by the neighboring aryl and sulfur substituents.[19]



Scheme 4 Proposed reaction mechanism.

One-electron oxidation of **III** by the eosin Y radical cation furnishes an electrophilic species which undergoes substitution in the presence of a large excess of DMSO (solvent).[20] A long radical chain mechanism is unlikely, as ^{1}H NMR monitoring showed that product formation stopped when the light source was removed.[21] We have investigated the nature of by-products. Thermal heterolytic cleavage of arenediazonium salts occurs at elevated temperatures (>40 °C) to give an aryl cation which is rapidly trapped by the nucleophilic solvent DMSO.[22] The resultant $[ArOSMe_2]^+$ was detected using ESI-MS.[21]

In summary, we have developed a new photocatalytic thiolation protocol in the presence of only 2 mol% eosin Y, which allows the facile synthesis of arylsulfides in good yields. The mild reaction conditions (green light, r.t.) tolerate various functional groups and can be applied to the conjugation with thiol-containing amino acids.

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