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Communication

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A Radical Smiles Rearrangement Promoted by Neutral Eosin Y as a Direct Hydrogen Atom Transfer Photocatalyst

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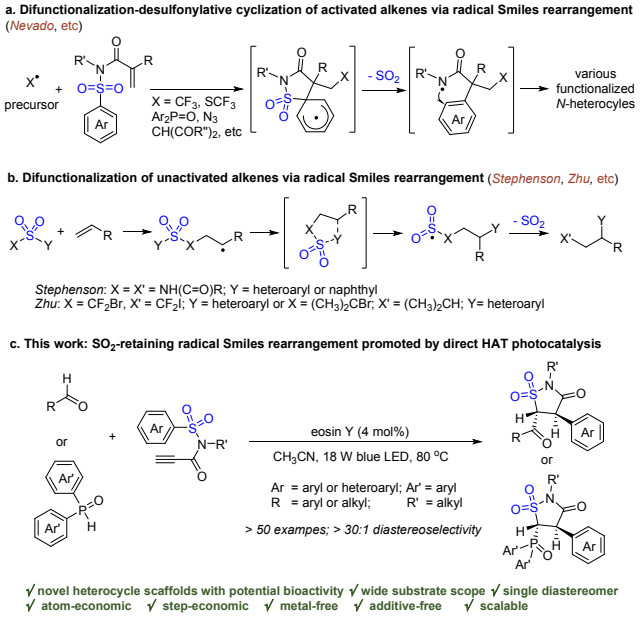
Supporting Information Placeholder

ABSTRACT: A visible light-mediated radical Smiles rearrangement has been achieved using neutral eosin Y as a direct hydrogen atom transfer (HAT) photocatalyst. Novel *N*-heterocycles as single diastereomers featuring an isothiazolidin-3-one 1,1-dioxide moiety are directly accessed by this method. A wide range of functional groups can be incorporated in the products by employing diverse aldehydes and *N*-(hetero)arylsulfonyl propiolamides. The transformation proceeds through a cascade of visible-light-induced HAT, 1,4-addition, Smiles rearrangement, 5-*endo*-trig cyclization and a reverse HAT process. Preliminary biological studies of the highly functionalized heterocyclic compounds suggest potential anti-cancer activity with some of the synthesized compounds.

The conventional Smiles rearrangement is an intramolecular nucleophilic aromatic substitution that occurs at the *ipso*-position of arylsulfones.[1] The aromatic substrates are typically activated by electron-withdrawing groups at the *ortho* or *para* positions. Since the seminal work of Speckamp, et al. to transpose the ionic conditions to radical chemistry,[2] the radical Smiles rearrangement has become a versatile strategy enabling the formal migration of (hetero)aryl and other unsaturated C–C bond moieties.[3] This radical rearrangement is capable of breaking various C(sp^2)–X (X = S, O, N, C) bonds that are not limited to sulfones. Distinct from ionic pathways, the presence of electron-withdrawing groups is not necessary in radical Smiles rearrangements. Although a stoichiometric amount of a radical initiator is required to trigger the radical process under relatively harsh conditions,[4] early examples of aryl migration have benefitted from this rearrangement. Recently, this strategy was extensively employed to realize difunctionalization of alkenes or alkynes under both transition-metal and photoredox catalysis.[5] Elegant approaches to access heterocycles have also been described.[6] Notably, the Nevado group used transition metal-catalyzed radical Smiles rearrangements to synthesize a series of *N*-heterocycles. Reactions of this sort normally employed tailored *N*-arylsulfonyl acrylamides as activated alkene substrates (Scheme 1a).[7] Difunctionalization of unactivated alkenes by photoredox catalysis was nicely illustrated independently by the Stephenson group[5a] and the Zhu group.[5b,5c] In these reactions, SO_2 serves as a traceless linker of two functional moieties (Scheme 1b). The arylsulfonyl group has been shown to represent a privileged aryl migrating source in Smiles rearrangements owing to its excellent reactivity and facile installation using commercially available arylsulfonyl chlorides.[3d] The Smiles rearrangement is followed by an entropically favored desulfonylation.[4,5] Retention of SO_2 to render a more atom-economic transformation remains rare.[8]

Scheme 1. Practical Radical Smiles Rearrangement-Based Transformations

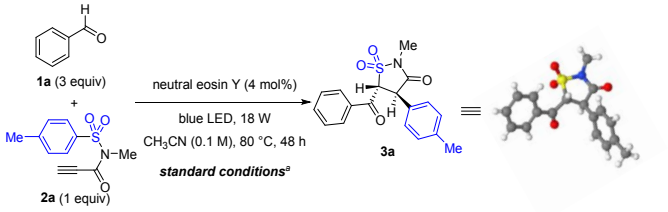


Our group recently developed a robust and versatile C–H functionalization protocol using neutral eosin Y as a direct hydrogen atom transfer (HAT) photocatalyst.[9] This efficient catalytic system enables facile access to a variety of carbon radicals in an extremely mild and green manner. We envisioned that radicals generated by this strategy would readily trigger subsequent cascade radical processes such as the

aforementioned Smiles rearrangement to access novel molecular scaffolds directly. We herein report that subjecting aldehydes or phosphine oxides and easily accessible *N*-arylsulfonyl propiolamides to neutral eosin Y-based direct HAT photocatalytic conditions provides unique densely functionalized isothiazolidin-3-one 1,1-dioxides with excellent diastereoselectivity (Scheme 1c). This approach retains SO_2 to construct potentially bioactive heterocycles, which are otherwise difficult to prepare. Bioactive compounds containing an isothiazolidin-3-one 1,1-dioxide moiety are shown in Figure S1.[10]

Our study was initiated by using benzaldehyde **1a** and *N*-tosyl propiolamide **2a** as model reactants. After extensive optimization of conditions (Table 1), neutral eosin Y (4 mol%) in CH_3CN under 18 W blue LED irradiation at 80 °C afforded heterocyclic product **3a** in 87% isolated yield (entry 1). The configuration of **3a** was unambiguously determined by single crystal X-ray diffraction analysis (Figure S2).[11] The elevated temperature of 80 °C was necessary to ensure an efficient transformation and high diastereoselectivity (>30:1). A mixture of diastereomers was obtained in much lower yield at room temperature (entry 2). The control experiments indicated that the *cis*-isomer **3a'** is not stable, which can easily epimerize to the more stable *trans*-isomer **3a** under heating or slightly acidic conditions (Scheme S2, Figure S9). Replacing the eosin Y photocatalyst by combinations of a photoredox catalyst and a HAT agent[12] resulted in little or no desired product (entries 3 and 4; for evaluation of more photocatalysts, see Table S1). Use of dianionic Na_2eosin Y led to decomposition of **1a** with no product detected (entry 5), which is consistent with our earlier recognition of neutral eosin Y as the active HAT photocatalyst.[9] On the other hand, product **3a** could be obtained in 50% yield using a different direct HAT photocatalyst tetra-*n*-butylammonium decatungstate (TBADT)[13] under UV irradiation (entry 6). An excess amount (3 equiv) of aldehyde proved to be essential to obtain products with high yields (entries 7 and 8). Acetone, *tert*-butanol and H_2O as solvents also gave the desired product, albeit with lower yields (entries 9–11). Control experiments in the absence of blue LED irradiation resulted in no reaction, confirming that light is essential (entry 12).

Table 1. Selected Optimization Results



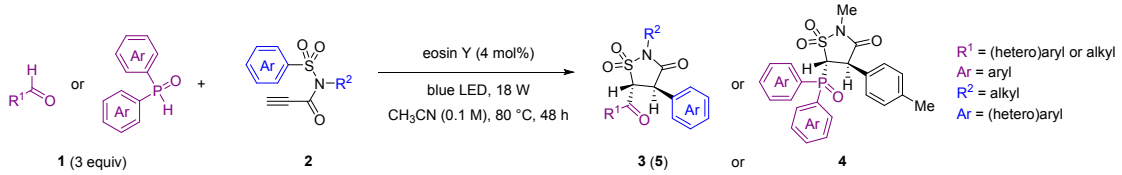
entry	deviation from standard conditions	conv. of **2a** (%)[b]	yield of **3a** (%)[b]	*d.r.* of **3a**[b]
1	none	100	89(87)	>30:1
2	room temperature instead of 80 °C	40	37	2:1
3	Mes-Arc$^+$$ClO_4^-$ (2 mol%)+HCl (5 mol%)	70	7	-
4	$Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2 mol%) + $PhCO_2Na$ (5 mol%)	80	0	-
5[c]	Na_2eosin Y (4 mol%) as the catalyst	100	0	-
6[d]	TBADT (4 mol%) as the catalyst	100	50	>30:1
7	2 equiv of **1a**	70	40	>30:1
8	4 equiv of **1a**	100	88	>30:1
9	acetone instead of CH_3CN	100	53	>30:1
10	*tert*-butanol instead of CH_3CN	100	80	>30:1
11	H_2O instead of CH_3CN	26	13	-
12	without blue LED light	0	0	-

[a]Standard conditions: **1a** (0.3 mmol), **2a** (0.1 mmol), eosin Y (4 mol%), and CH_3CN (1 mL) in a Schlenk tube (20 mL) at 80 °C under blue LED (18 W) irradiation. Freeze-pump-thaw was repeated 3 times to remove air and fill argon into the reaction vessel. [b]Conversions and diastereoselectivities were determined by analysis of the crude ^{1}H NMR using 1,3,5-trimethoxylbenzene as an internal standard; an isolated yield is shown in parentheses. [c]*N*-methyl-tosylamine was formed. [d]The reaction was performed under 365 nm LED irradiation.

With the optimized conditions in hand, the scope of aldehydes was examined (Table 2, top). A diverse set of aromatic aldehydes, regardless of their electronic properties were found to be compatible with our protocol and produced the corresponding densely functionalized isothiazolidinones (**3b**–**3q**) as single diastereomers in good yields. Various functional groups such as hydroxyl (**3d**), amide (**3e**), boronic ester (**3j**), ester (**3c**; **3k**), halide (**3g**–**3i**; **3o**–**3p**) and cyanide (**3m**–**3n**) groups were well tolerated. The aromatic aldehyde substrates bearing substituents at *ortho* or *meta* positions (**3n**–**3q**) were also suitable candidates, indicating the feasibility of further derivatization. Aliphatic aldehydes containing either a branched or linear alkyl chain successfully participated in this cascade transformation to provide **3r**–**3v** in moderate to good yields. Decarbonylated product was not observed although a related study[14] indicates that the facile decarbonylation of branched acyl radical could occur. It is worth noting that various heterocyclic aldehydes could also be employed and delivered heterocycle-enriched products (**3w**–**3y**) in good yields. As an initial effort to extend this HAT catalytic system beyond C–H substrates, we found that phosphine oxides turned out to be suitable, providing rapid access to phosphine-containing isothiazolidiones **4a**–**4e** in moderate to good yields (Table 2, middle). Electron-withdrawing, electron-donating and sterically demanding substituents in the diaryl phosphine oxides were well tolerated.

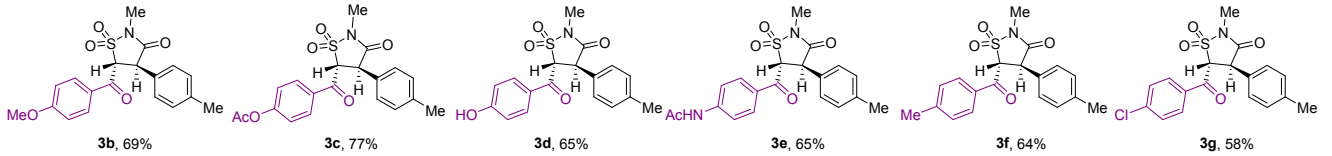
The scope with respect to *N*-arylsulfonyl propiolamides was subsequently investigated (Table 2, bottom). Systematic modification of the arylsulfonyl moiety was feasible, accommodating both electron-rich (**5c**–**5f**) and electron-poor substituents (**5g**–**5i**). The reaction also proceeded smoothly with *meta* or *ortho* substituents on the arylsulfonyl groups (**5j**–**5m**). Notably, this cascade protocol is applicable to *N*-heteroarylsulfonyl propiolamide, direct joining the pyridine and thiophene moiety to the isothiazolidione scaffold (**5n**–**5o**). Changing the *N*-methyl substituent to *N*-4-pentenyl (**5p**) or *N*-cyclohexyl (**5q**) was also feasible. The former delivered the desired isothiazolidinone product (**5p**) selectively in spite of the possibility of an alternative cyclization at the terminal alkene.

Table 2. Substrate Scope of Aldehydes, Phosphine Oxides and *N*-(Hetero)Arylsulfonyl Propiolamides

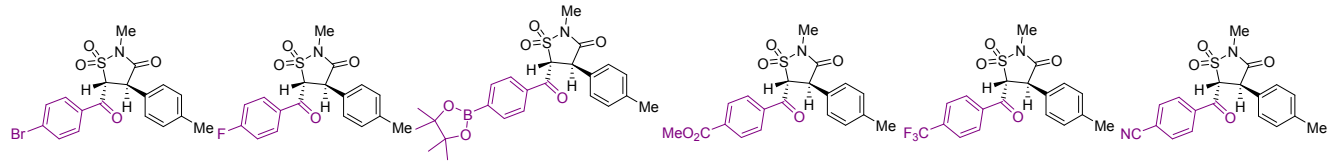


1 (3 equiv) **2** **3** (**5**) or **4**

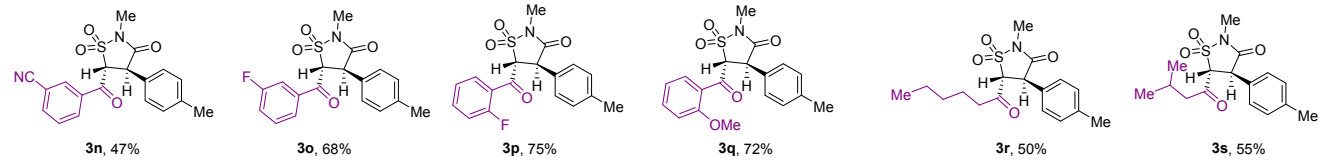
Scope of aldehydes[a]



3b, 69% **3c**, 77% **3d**, 65% **3e**, 65% **3f**, 64% **3g**, 58%

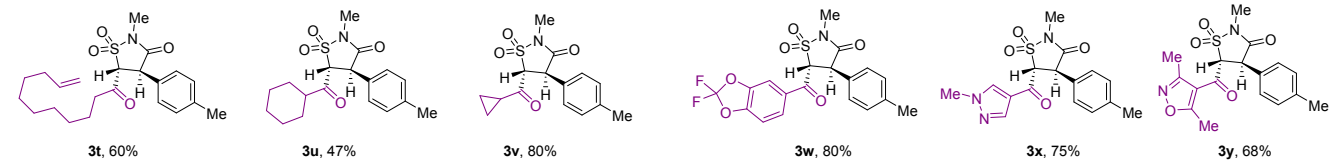


3h, 60% **3i**, 95% **3j**, 56% **3k**, 76% **3l**, 79% **3m**, 53%



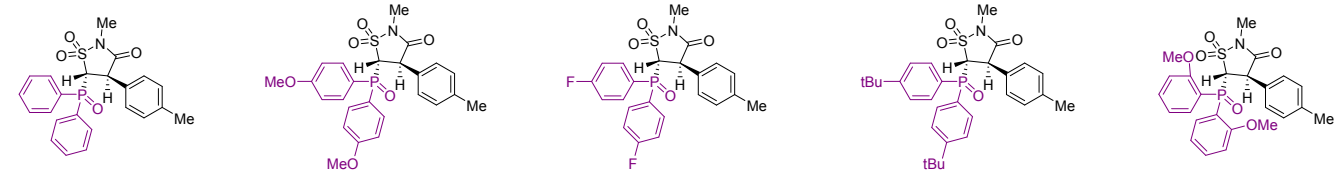
3n, 47% **3o**, 68% **3p**, 75% **3q**, 72% **3r**, 50% **3s**, 55%

heterocycle-containing aldehyde



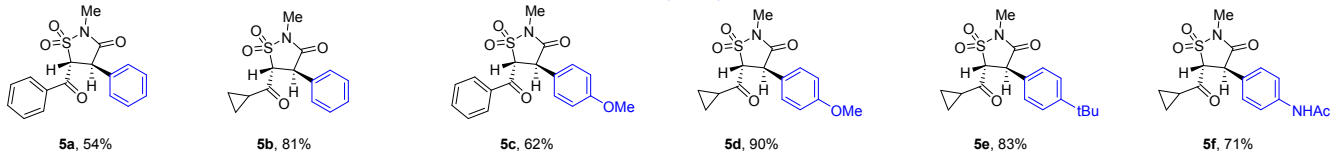
3t, 60% **3u**, 47% **3v**, 80% **3w**, 80% **3x**, 75% **3y**, 68%

Scope of phosphine oxides[a,b]

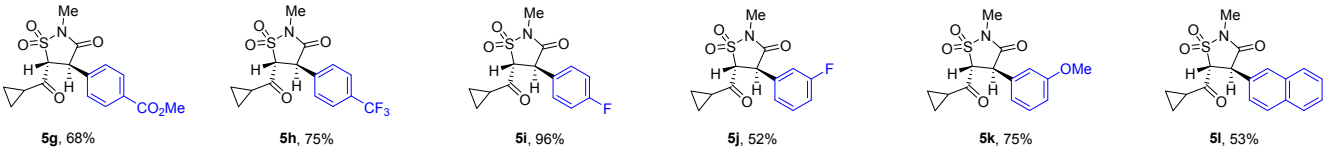


4a, 70% **4b**, 64% **4c**, 67% **4d**, 44% **4e**, 59%

Scope of *N*-(hetero)arylsulfonyl propiolamides[a]



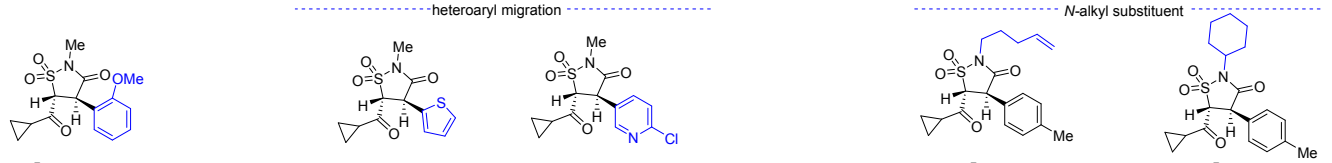
5a, 54% **5b**, 81% **5c**, 62% **5d**, 90% **5e**, 83% **5f**, 71%



5g, 68% **5h**, 75% **5i**, 96% **5j**, 52% **5k**, 75% **5l**, 53%

heteroaryl migration

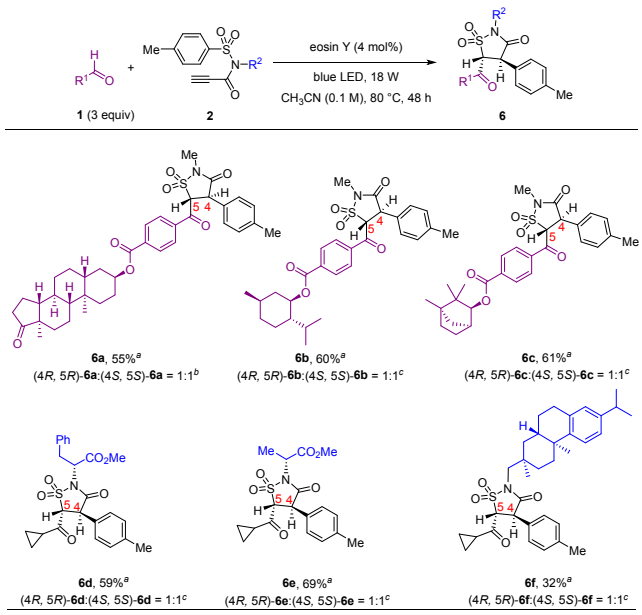
N-alkyl substituent



5m, 65% **5n**, 88% **5o**, 50% **5p**, 46% **5q**, 48%

[a]Reactions were performed under the standard conditions described in Table 1. Single diastereomers were obtained in all cases and isolated yields are shown. [b]Reations were performed at room temperature under otherwise the same conditions as the standard conditions described in Table 1.

Table 3. Incorporation of Complex Molecules



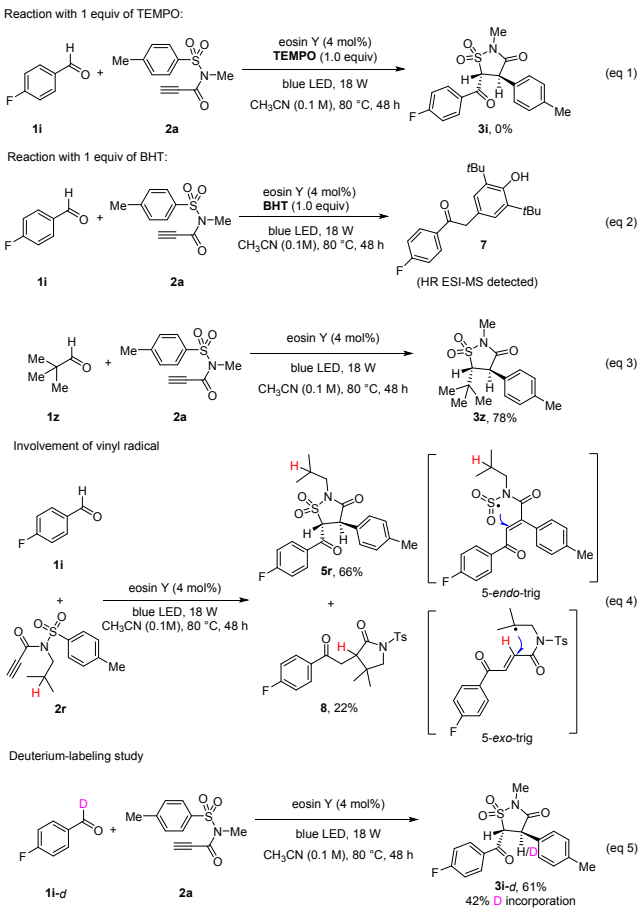
[a]Reactions were performed under the standard conditions in Table 1. A mixture of two isomers was obtained and overall isolated yields were shown. Undrawn isomer denotes (4*S*,5*S*) configuration at the isothiazolidione moiety. Configuration of other chiral centers was identical for the two isomers. [b]Ratio of the two isomers was estimated by chiral HPLC analysis. [c]Ratio of the two isomers was determined by analysis of the crude ^{1}H NMR spectra.

Encouraged by the broad substrate scope of this mild cascade transformation, we sought to extend the reaction to derivation of complex molecules (Table 3). Aldehydes derived from natural products such as epiandrosterone, (-)-menthol, (+)-fenchol participated in this transformation to afford **6a**-**6c** in moderate yields. In addition, *N*-arylsulfonyl propiolamides prepared from (+)-dehydroabietylamine, *D*-alanine and *D*-phenylalanine also delivered the corresponding products **6d**-**6f** smoothly. Although four diastereoisomers could be generated theoretically in each reaction, only two isomers in an approximate 1:1 ratio determined by ^{1}H NMR or HPLC analysis, were generated as exclusive *trans*-configurations obtained with the isothiazolidinone moiety (4-C *vs* 5-C). To further demonstrate the synthetic utility of the established protocol, the cascade reaction was amenable to scale up to gram-scale (Scheme 2), illustrating the robustness of this protocol.

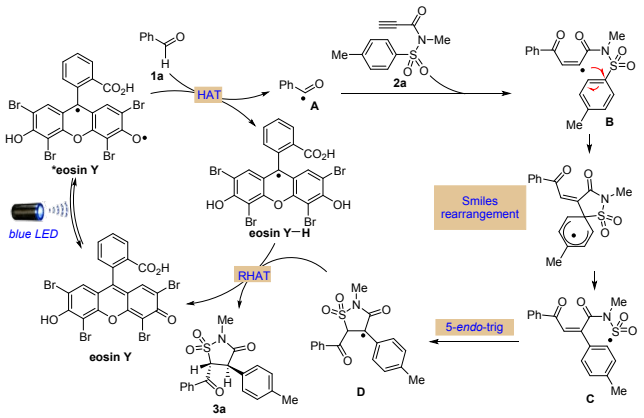
Scheme 2. Gram Scale Synthesis

Control experiments were conducted to probe the reaction mechanism (Scheme 3). Addition of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT) completely stopped the reaction (eq 1 and 2), and the adduct of BHT and the 4-fluorobenzoyl radical (**7**) was detected by high-resolution electrospray ionization mass (HR ESI-MS) spectrometric analysis (Figure S4).[15] *Tert*-butyl group instead of pivaloyl group was incorporated in the isothiazolidione skeleton of **3z** using pivalaldehyde (**1z**) as the starting aldehyde, due to facile decarbonylation of pivaloyl radical to give the more stable *tert*-butyl radical (eq 3).[16] Collectively, these findings support the involvement of acyl radicals in the present reaction process. We then attempted to prove the generation of a vinyl radical upon addition of the acyl radical to the C≡C triple bond (eq 4). Subjection of *N*-tosyl-*N*-isobutyl propiolamide (**2r**) to the reaction conditions afforded an isothiazolidinone (**5r**), together with the γ-lactam **8** in 22% yield. While the formation of **5r** resulted from a Smiles rearrangement and 5-*endo*-trig cyclization of the transient vinyl radical, the generation of **8** could be rationalized by a competitive pathway involving 1,5-HAT and 5-*exo*-trig cyclization,[17] which support the presence of the transient vinyl radical intermediate. A deuterium-labelling study was performed using 4-fluorobenzaldehyde-*d* (**1i**-*d*) in which the aldehyde C–H was deuterated (eq 5). The reaction gave **3i**-*d* in which 42% deuteration was found at C-4 of the isothiazolidinone ring. This deuterium incorporation in the final product can originate from an initial HAT step from aldehyde **1i**-*d*. The loss of deuterium is likely due to the trace amount of water present in the reaction mixture (Figure S5). In addition, both light on/off experiments and a quantum yield determination (Φ = 0.17) disfavored a chain mechanism (Figure S6, eq S14).

Scheme 3. Mechanistic Investigation



Scheme 4. Proposed Mechanism



Based on all the experimental results and earlier literature reports,[9] a plausible mechanism was proposed as illustrated in Scheme 4. The excited *eosin Y undergoes a HAT with aldehyde **1a** to deliver an acyl radical **A**. Upon addition of this acyl radical to *N*-arylsulfonyl propiolamide **2a**, a vinyl radical species **B** is generated which initiates the subsequent Smiles rearrangement to afford a postulated sulfonyl radical **C**. Radical **C** undergoes a 5-*endo*-trig cyclization to deliver the α-carbonyl benzylic radical **D**. Finally, **D** is capable of regenerating eosin Y via a reverse HAT (RHAT), simultaneously furnishing the isothiazolidione product **3a**. Even though we cannot exclude the possibility of a single electron transfer (SET) between radical **D** and eosin Y-H, the density functional theory (DFT) calculations indicated that the SET pathway was unlikely as the relative free energy barrier was 10 kcal/mol higher than that of the RHAT pathway (Figure S9).

The isothiazolidinone scaffold has been reported to be active toward PTP1B,[10b,18] an important target for the development of anti-cancer drugs.[19] Preliminary evaluation of the anti-cancer activity of selected synthesized heterocyclic compounds was conducted in a human breast cancer cell line (MCF7) and a cervical cancer cell line (HeLa) (Figure S10). It was found that modification of the isothiazolidinone skeleton can affect the activity dramatically. The preliminary results (Table S2) indicated that **3y** is active in various cell lines including MCF7 (IC_{50} = 7.18 μM), HeLa (IC_{50} = 10.08 μM), human lung cancer cell line A549 (IC_{50} = 20.62 μM) and the colon cancer cell line Caco-2 (IC_{50} = 32.18 μM). Further bioactive investigation of this unique class of compounds is currently ongoing in our laboratory.

In conclusion, an efficient radical Smiles rearrangement initiated by neutral eosin Y-based HAT photocatalysis is developed. The merits of this transformation include atom- and step-economic, metal- and additive-free, excellent selectivity, and generation of otherwise difficultly generated heterocycle scaffolds. Practical modification of either starting substrate leads to the direct access to a variety of highly functionalized isothiazolidinone compounds, which are potentially biologically interesting molecules. This study highlights the opportunity of neutral eosin Y-based direct HAT photocatalysis to access new chemical space via radical rearrangement transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

General procedures, analytical data, and NMR spectra (PDF)

X-ray data for compound **3a** (CIF)

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Notes

The authors declare no competing financial interests.

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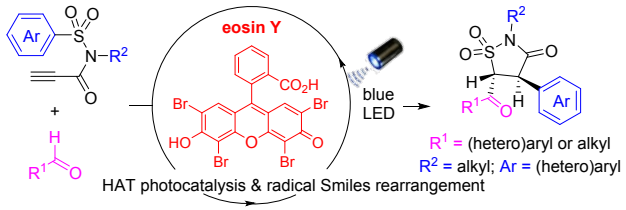

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