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Visible light promoted metal and oxidant-free stereoselective synthesis of functionalized succinimides from aza-1,6-enynes†

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An operationally simple approach has been developed for synthesizing diversely functionalized succinimides under transition-metal and oxidant-free conditions in PEG-400. The developed strategy is promoted by visible light and proceeds *via* radical cascade iodo-sulfonylation of aza-1,6-enynes in an atom economical manner with excellent stereoselectivity. Control experiments well support the proposed pathway for the reaction. The reaction's expedient features include operational simplicity, eco-friendly solvent, atom economy, and functional group tolerance with a broad substrate scope.

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Sustainability spotlight

Considering global environmental concerns, the development of efficient protocols using green solvents and transition-metal-free, atom-economical organic transformations to construct valuable small molecules in a single step is a common objective for both researchers and the pharmaceutical industry.

Introduction

Considering global environmental concerns, the development of efficient protocols using green solvents for organic transformations to construct valuable heterocycles in a single step is a common objective for both researchers and the pharmaceutical industry.¹ In recent years, the use of environmentally friendly alternative reaction media, such as ionic liquids² and polyethylene glycol (PEG),³ has been widely explored. In recent years, PEG has been widely used in a variety of organic reactions over toxic organic solvents due to its biodegradable, biocompatible, and non-toxic characteristics.⁴ Several C–C bond-forming reactions,⁵ oxidation,⁶ reduction,⁷ and substitution reactions^{8,9} have been reported using PEG as a solvent. PEG was also used as a medium for free-radical organic reactions.¹⁰

The succinimide motif is an intriguing member of *N*-containing heterocycles that are crucial to many biologically active natural products and active pharmaceutical ingredients (APIs). It is a component of several pharmaceutically active compounds having activities such as CNS depressant, analgesic, antitumor,

cytostatic, anorectic, nerve conduction blocking, antispasmodic, bacteriostatic, muscle relaxant, hypotensive, antibacterial, antifungal, anticonvulsant and anti-tubercular properties.¹¹ Succinimide analogues like phensuximide, methsuximide, and ethosuximide are known for their effect as efficient antiepileptic drugs (AEDs).¹² Succinimide scaffolds have also been found to be potential drug candidates for treating a series of neurodegenerative diseases and for promoting amyloid fibrillation of hen eggs.^{13,14} Tecovirimat was the first drug utilized for smallpox¹⁵ and tivantinib is used for solid tumours by inhibiting the activity of *c-met*¹⁶ (Fig. 1). The iodo functionality introduced provides a useful route for structural elaboration to generate complex molecules.

Numerous methodologies for the synthesis of succinimides have been reported in the literature. However, these approaches exhibit constraints including extended reaction durations, diminished yields and reliance on costly metal catalysts.¹⁷ Owing to their significant applicability in drug discovery and their role as pharmaceutical scaffolds, synthesis of

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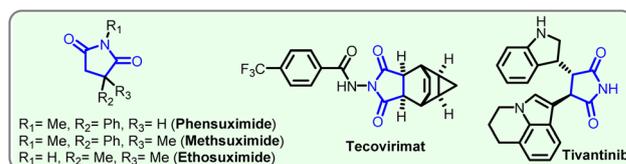
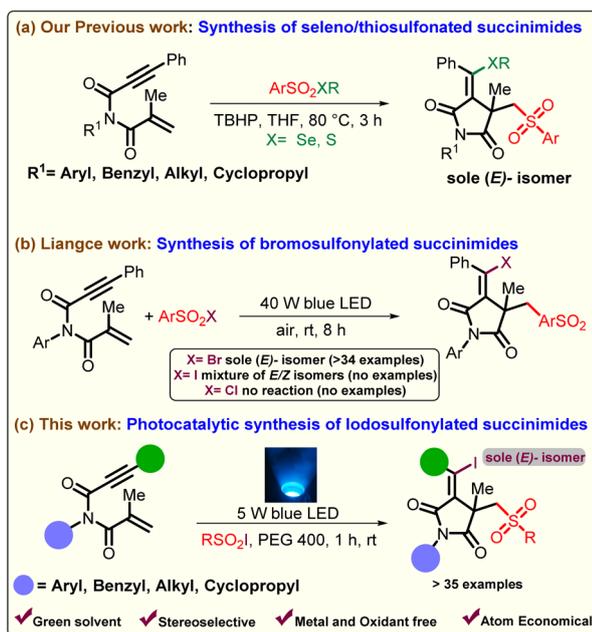
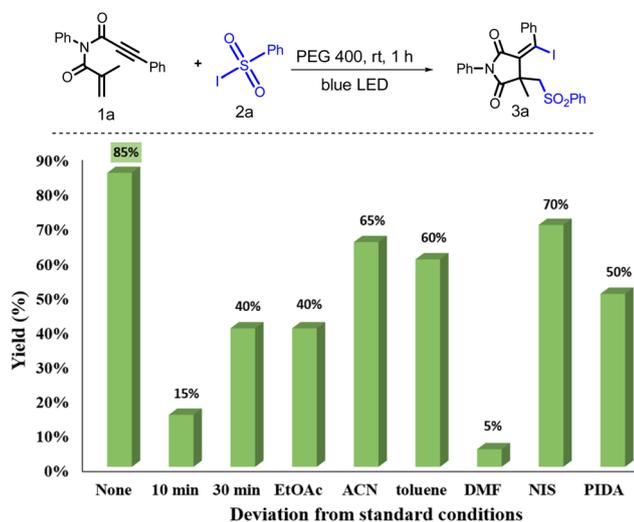


Fig. 1 Representative biologically active succinimides.





Scheme 1 Radical cascade synthesis of succinimides.

Scheme 2 Optimization graph.^a Reaction conditions: reactions were performed using 0.346 mmol (1.0 equiv.) of **1** and 0.415 mmol (1.2 equiv.) of **2** in 2.0 mL of PEG 400 under a blue LED for 1 h in an air atmosphere. NIS and PIDA iodine sources were optimized using sodium benzenesulfinate salt.

functionalized succinimides is critical. Radical cascade cyclization of 1,*n*-enynes has emerged as an attractive strategy for constructing polycyclic compounds with high atom and step economy.¹⁸ The radical cascade strategy has been successfully implemented for the synthesis of a variety of heterocyclic motifs like benzofurans, thiophenes, quinolines, indenones, and spiro-polycyclic frameworks.¹⁹ The sulfone group is an important functional group that exists widely in various bioactive compounds, natural products, and organic functional

materials.²⁰ Additionally, halogen groups are prominent units found in pharmaceutical and materials chemistry.²¹

In recent times, effective synthetic methods utilizing 1,6-enynes²² and 1,6-diynes²³ have emerged for the synthesis of complex fused ring frameworks. Due to the significant emphasis placed on environmental concerns, there has been a pressing need for the development of environmentally friendly and mild synthetic methodologies involving functionalization and cyclization.²⁴ We described a metal-free synthesis of di-functionalized succinimides, achieving good to excellent yields with outstanding stereoselectivity (Scheme 1a).²⁵ Subsequently, while we were preparing this manuscript, Rong and coworkers reported the synthesis of succinimide derivatives using sulfonyl bromides and 1,6-enynes after a reaction time of 8 h under 40 W blue LED irradiation (Scheme 1b).²⁶ The findings were limited to sulfonyl bromides, as the use of sulfonyl iodides resulted in a mixture of *E/Z* isomers, and the reaction failed to proceed with sulfonyl chlorides. No product was obtained when employing ACN as solvent. The substrate scope for sulfonyl bromides was also limited to a few substrates, with no incorporation of heteroatom-containing sulfonyl bromides. Intrigued by these findings, we planned a photocatalytic two component synthesis of iodo-sulfonated succinimides. The broad substrate scope includes aliphatic and strained ring (C_p) derivatives.

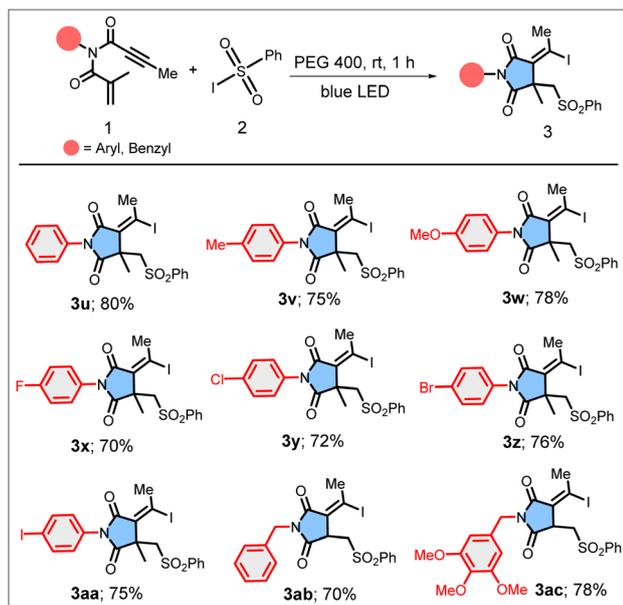
A literature survey revealed that radical cascade cyclization using aza-1,6-enynes for the synthesis of highly functionalized succinimides has not been much explored and remains a challenge. In continuation of our efforts in this laboratory,²⁷ we envisioned that difunctionalized iodo sulfonated succinimides could be photocatalytically synthesized directly from aza-1,6-enynes and sulfonyl iodides in a radical cascade manner using a green and environmentally friendly solvent, PEG, at rt (Scheme 1c).

Results and discussion

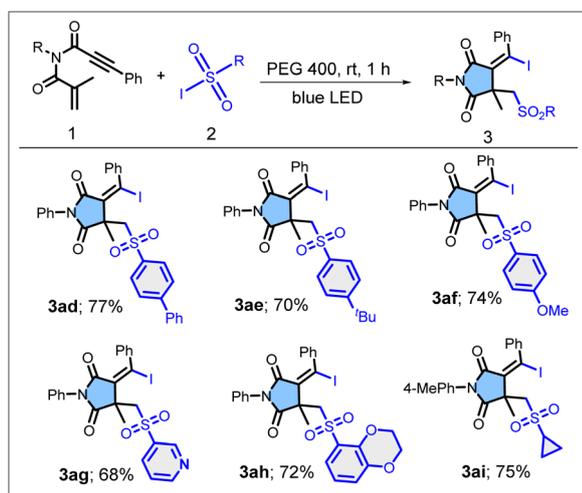
We commenced our investigation by employing *N*-phenyl-*N*-(3-phenylpropionyl) methacrylamide (**1a**) with benzenesulfonyl iodide (**2a**) as a model substrate (Scheme 2). The reaction of **1a** (1.0 equiv.) with **2a** (1.2 equiv.) using PEG 400 as solvent under a blue LED for 1 hour afforded the product **3a** in 85% yield. The reaction showed high diastereoselectivity as the sole *E*-isomer of **3a** was formed. Product **3a** was formed in 15% and 40% yields after reaction times of 10 and 30 minutes, respectively. Next, we screened different solvents like ethyl acetate, ACN, toluene and DMF, but they all resulted in lower yields (5–65%) of the product, which shows that PEG-400 was the best suitable solvent for this conversion. Next, different iodine sources were screened, and NIS produced the product in 70% yield, while PIDA only gave 50% yield of the product when used along with sodium benzenesulfinate salt.

The attainment of the optimal conditions was subsequently followed by the execution of the stereoselective iodo-sulfonylation of different aza-1,6-enynes (Scheme 3). Gratifyingly, tosyl iodides can be stereoselectively added to the aza-1,6-enynes to yield di-functionalized succinimide derivatives in excellent



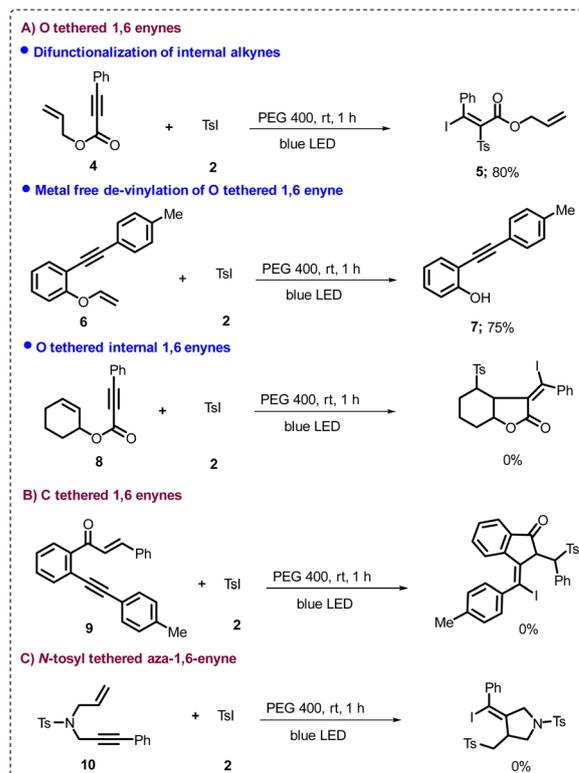


Scheme 4 Substrate scope of *N*-methacryloyl-*N*-aryl/benzylbut-2-ynamide^a. ^aReactions were performed using 0.440 mmol (1.0 equiv.) of 1 and 0.528 mmol (1.2 equiv.) of 2 in 2.0 mL of PEG 400 under a blue LED for 1 h.



Scheme 5 Substrate scope of sulfonyl-iodides^a. ^aReactions were performed using 0.346 mmol (1.0 equiv.) of 1 and 0.415 mmol (1.2 equiv.) of 2 in 2.0 mL of PEG 400 under a blue LED for 1 h in an air atmosphere.

The reaction of **1a** with **2a** under the optimized reaction conditions in the presence of 3.0 equivalents of BHT showed complete inhibition of product **3a** (Scheme 7A). This experiment suggested that the reaction is proceeding *via* the radical pathway. To showcase the synthetic utility, the scale-up synthesis of **3a** was studied using **1a** (3.4 mmol) and **2a** (4.08 mmol) as the representative substrates (Scheme 7B). The reaction afforded product **3a** in 75% yield. To illustrate the synthetic versatility of this protocol, the Pd-catalyzed C–C cross-coupling of **3a** with



Scheme 6 Screening of other heteroatom tethered 1,6-enynes.

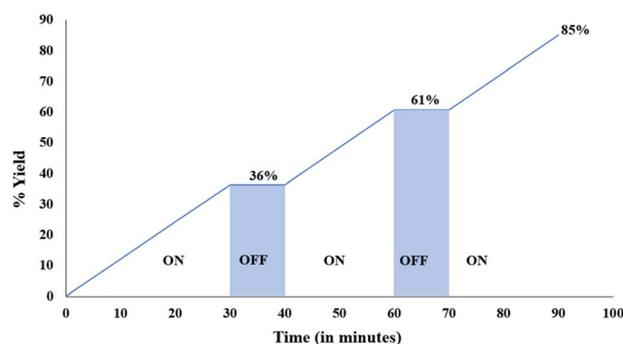


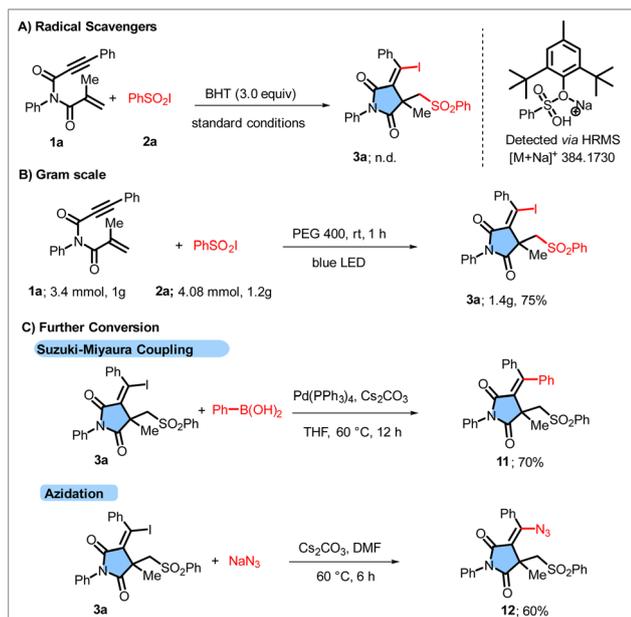
Fig. 2 Light irradiation on/off experiment.

phenylboronic acid was performed, which yielded the product **4** in 70% yield. The azidation reaction of **3a** with NaN_3 in the presence of Cs_2CO_3 yielded azidated product **6** in 60% yield.

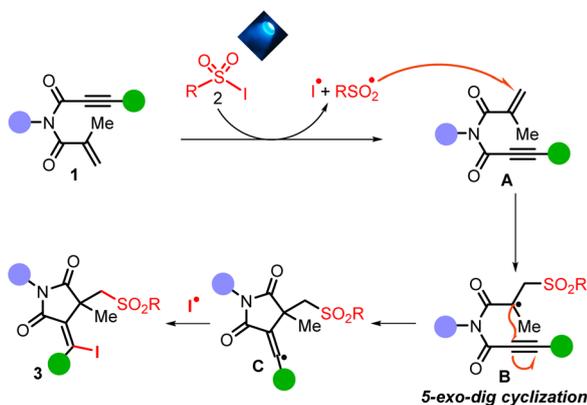
Based on the experimental findings and the available literature,²⁹ a plausible mechanism for the reaction has been proposed, as shown in Scheme 8. The reaction initiates with the photocatalytic cleavage of sulfonyliodides into iodine and sulfonyl radicals, which has been confirmed using radical trapping experiments. The sulfonyl radical attacks the aza-1,6-enyne **A** to give **B**, which undergoes 5-*exo*-dig cyclization to afford the vinyl radical intermediate **C**. Radical **C** is trapped by the iodine radical to yield the stereoselective product **3**.

In conclusion, the chemistry described herein provides a facile, atom-economical, eco-friendly solvent, and





Scheme 7 (a) Control experiments, (b) gram scale synthesis and (c) further applications.



Scheme 8 Plausible reaction mechanism.

photocatalyzed approach for the synthesis of highly functionalized succinimides in good to excellent yields in a radical cascade manner. The developed protocol provides access to *E*-iodo-sulfonylated succinimides with high levels of stereoselectivity and tolerates a variety of functional groups. From a synthetic point of view, the developed chemistry involves a one-pot transformation of easily accessible starting materials into a functionalized and interesting class of succinimides. Iodine atoms serve as excellent leaving groups, facilitating various organic reactions such as palladium-catalyzed cross-coupling reactions and other organic transformations. This makes iodine a valuable synthon for the functionalization of organic molecules. The plausible reaction mechanism *via* the radical cascade pathway has been well supported by the control experiments.

Data availability

Data for all the synthesized compounds, including ^1H NMR, ^{13}C NMR, HRMS, and XRD, are given in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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