RSC Sustainability

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Sustainability*, 2025, **3**, 592

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

Shivam A. Meena,‡[a] Deepika Thakur,‡[a] Debanik Panda,[a] Rahul Ranjan[ac] and Akhilesh K. Verma *[ab]

Received 30th November 2024
Accepted 16th December 2024

DOI: 10.1039/d4su00753k

rsc.li/rscsus

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 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.

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 liquids[2] 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 smallpox[15] 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

[a]*Department of Chemistry, University of Delhi, Delhi-110007, India. E-mail: averma@acbr.du.ac.in*

[b]*Institution of Eminence (IoE), University of Delhi, Delhi-110007, India*

[c]*Netaji Subhas University of Technology, Delhi-110078, India*

† Electronic supplementary information (ESI) available. CCDC 2356138. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4su00753k

‡ These authors contributed equally to this work.

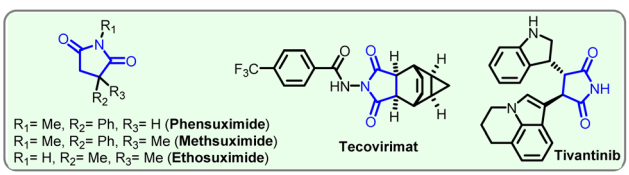
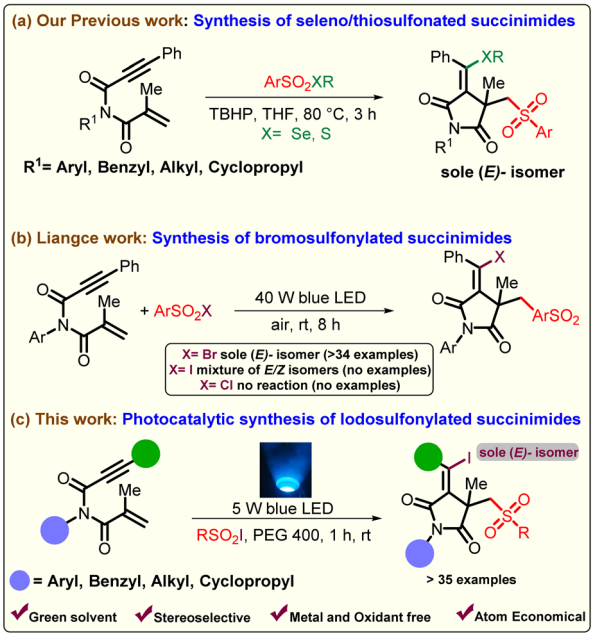
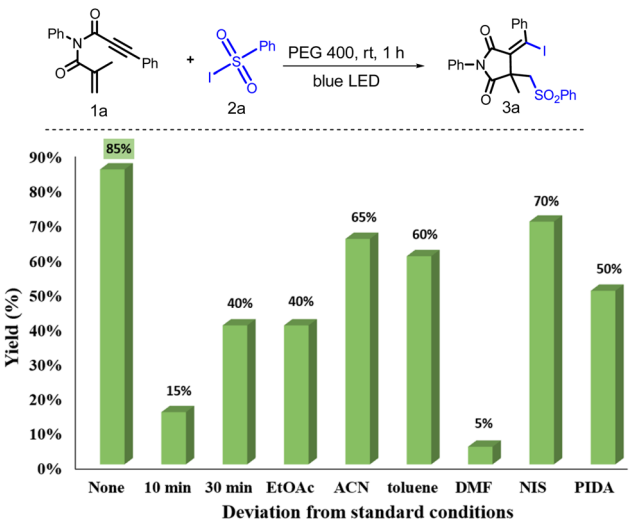


Fig. 1 Representative biologically active succinimides.



Scheme 1 Radical cascade synthesis of succinimides.



Scheme 2 Optimization graph[a]. [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]

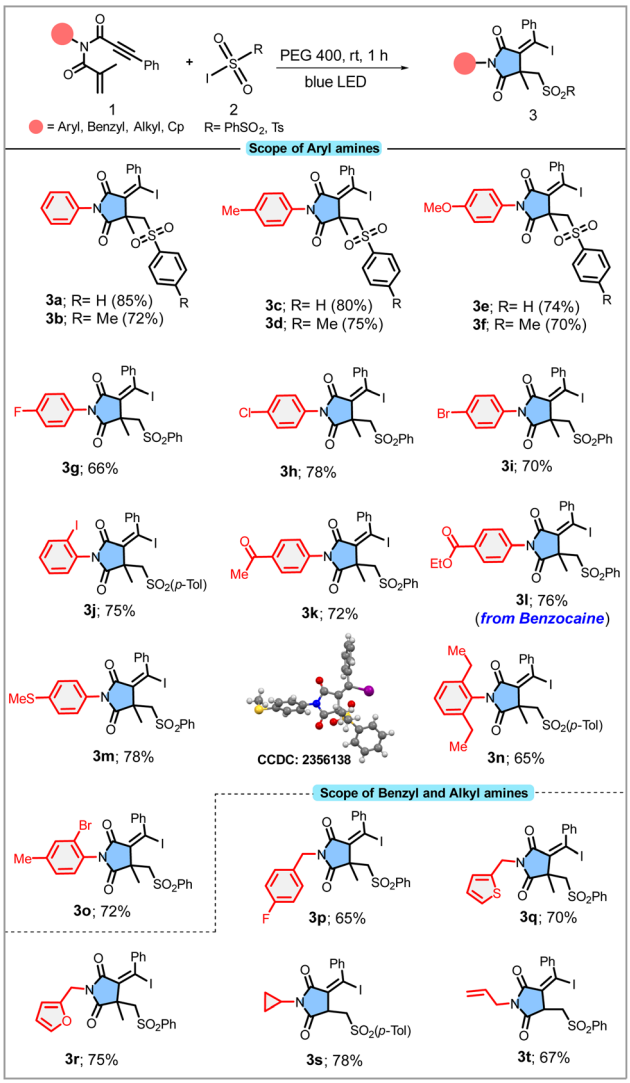
In recent times, effective synthetic methods utilizing 1,6-enynes[22] and 1,6-diynes[23] have emerged for the synthesis of complex fused ring frameworks. Due to the significant emphasis placed on environmental concerns, there has been a pressing need for the development of environmentally friendly and 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-sulfonylated 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-phenylpropioloyl)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, tosyliodides can be stereoselectively added to the aza-1,6-enynes to yield di-functionalized succinimide derivatives in excellent



Scheme 3 Substrate scope of aza-1,6-enynes[a]. [a]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. [b]Gram scale synthesis.

yields. The *N*-phenyl containing **1a** and *N*-(*p*-tolyl) containing substrate **1b** reacted smoothly with both benzenesulfonyl iodide and tosyl iodide to give the products **3a–d** in 72–81% yields. The reaction of electron rich *p*-OMe group **1c** with benzenesulfonyl iodide and tosyl iodide afforded the products **3e** and **3f** in 74% and 70% yields, respectively. Electron deficient *p*-F containing substrate **1d** reacted smoothly with benzenesulfonyl iodide to deliver the product **3g** in 66% yield.

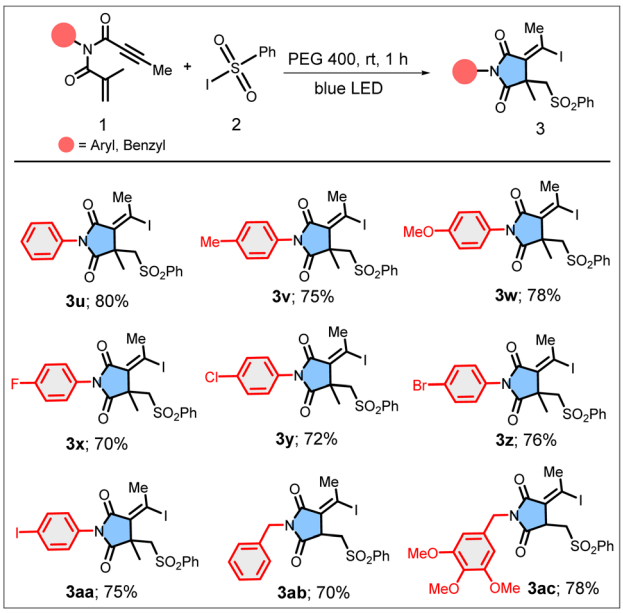
Next, we screened benzyl and aliphatic amines using our standard reaction conditions and we found that 4-fluorobenzylamine containing substrate **1m** under optimized conditions reacted smoothly, yielding product **3p** in 65% yield. Heteroatom, thiophene **1n** and furan **1o** containing benzyl amine afforded the corresponding products **3q** and **3r** in 70% and 75% yields respectively. Further, *p*-Cl **1e** and *p*-Br **1f** containing substrates gave the products **3h** and **3i** in 78% and 70% yields, while *o*-I **1g** substituted gave **3j** in 65% yield. Pleasingly, 4-acetylphenyl containing substrate **1h** was also a suitable partner for this conversion, resulting in the product **3k** in 72% yield. Fascinatingly, the aza-1,6-enyne tethered with benzocaine **1i**, a local anesthetic,[28] reacted smoothly under the standard conditions for this transformation to deliver product **3l** in 76% yield. A substrate having *p*-methylthiophenyl group **1j** afforded the product **3m** in 78% yield. Di-substituted substrates having 2,6-diethylphenyl group **1k** and 2-bromo-4-methylphenyl group **1l** gave the products **3n** and **3o** in 65% and 72% yields, respectively, and products **3q** and **3r** in 70% and 75% yields, respectively. Strained cyclopropyl ring containing substrate **1p** gave the product **3s** in 78% yield. To our delight, allylamine containing substrate **1q** yielded product **3t** in a yield of 67%.

We next extended our protocol to but-2-ynamide using the standard reaction conditions and gratifyingly we found that they were also suitable substrates for this conversion. Phenyl, *p*-Me and *p*-OMe substrates **1r–1t** gave the corresponding products **3u–3w** in 75–80% yields (Scheme 4). Halogen containing *p*-F, *p*-Cl, *p*-Br and *p*-I substrates **1u–1x** afforded the corresponding substrates **3x–3aa** in 70–76% yields. Further, benzyl group containing **1y** yielded **3ab** in 70% yield, while 3,4,5-trimethoxy benzyl group **1z** smoothly produced **3ac** in 78% yield.

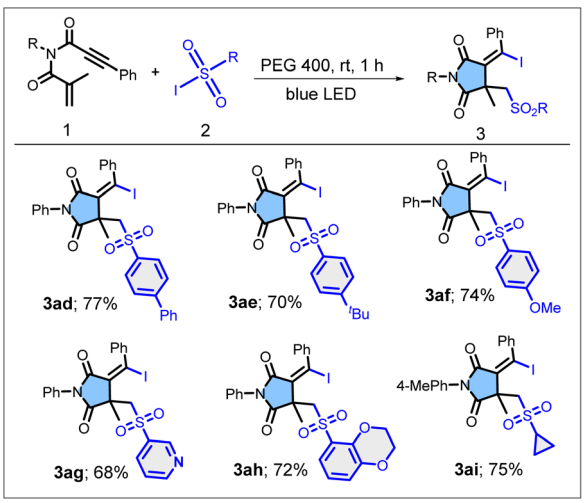
We further investigated the scope of sulfonyl iodides and found that several sulfonyl iodides were compatible with this conversion (Scheme 5). Substrates containing biphenyl sulfonyl iodides **2c** reacted well under optimized conditions to yield **3ad** in 77% yield. Substrates containing electron releasing groups ^{t}Bu and 4-OMe generated the corresponding products **3ae** and **3af** in 70% and 74% yields, respectively. To our delight, electron deficient pyridine and 1,4-dioxane containing sulfonyl bromides smoothly transformed into **3ag–3ah** in 68–72% yields. Intriguingly, aliphatic tosyl iodide having a strained cyclopropyl ring was also suitable for this conversion, yielding product **3ai** in 75% yield.

Intrigued by our prior substrate scope, we extended our methodology to other heteroatom tethered 1,6-enyne derivatives. When we used an *O*-tethered 1,6-enyne, we obtained a bifunctionalized alkyne product without cyclization (Scheme 6A). We observed a metal free devinylation of 2-(vinyloxy)benzene to obtain product **7** in good yield when **6** was exposed to the standard reaction conditions. Further, the internal alkene containing 1,6-enyne failed to yield the desired product. Unfortunately, C-tethered 1,6-enyne **9** failed to yield the desired product after 1 h. The *N*-tosyl tethered 1,6-enyne was also not a suitable substrate for this conversion, which shows that the presence of the carbonyl group (enone/ynone) is necessary for this conversion.

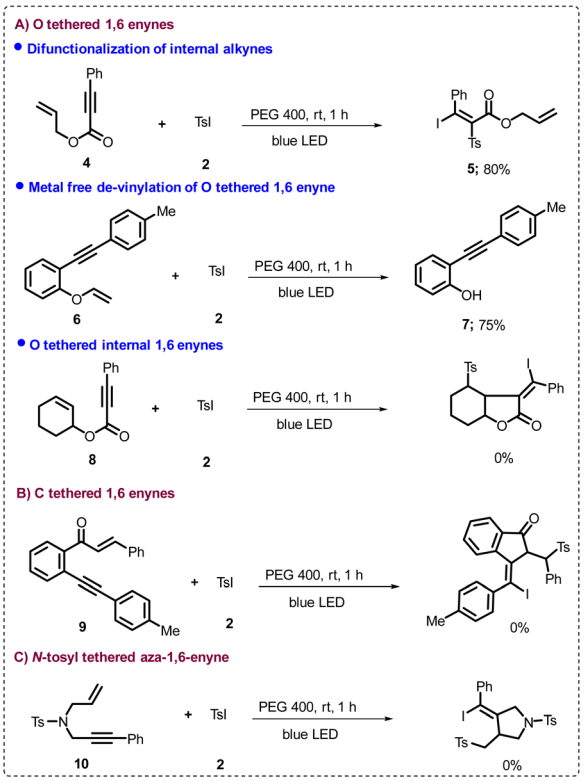
To establish the dependence of the reaction on photolytic conditions, an intermittent illumination experiment was performed and a correlation was plotted (Fig. 2). The reaction vessel was irradiated alternately with exposure to blue light and darkness. No product formation was observed in the dark phase, establishing the light-dependent nature of the reaction. To further gain insight into the reaction mechanism, we carried out some control experiments (Scheme 7). To probe the radical pathway, the reaction was performed in the presence of BHT under optimized reaction conditions.



Scheme 4 Substrate scope of *N*-methacryloyl-*N*-aryl/benzylbut-2-ynamide[a]. [a]Reactions 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]. [a]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.



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

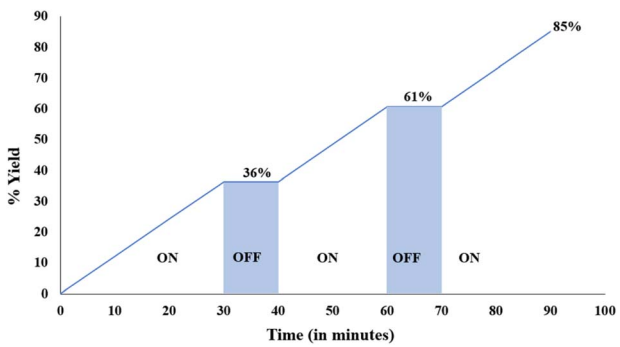
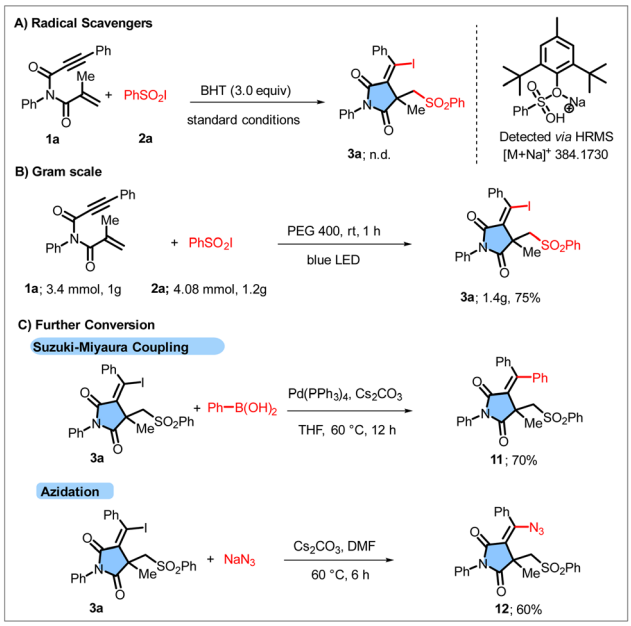


Fig. 2 Light irradiation on/off experiment.

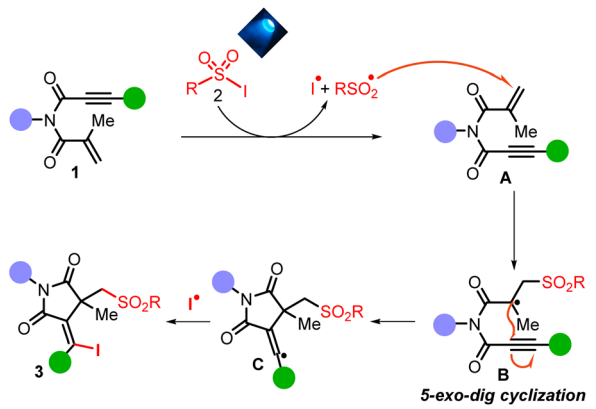
The reaction of **1a** with **2a** under the optimized reaction conditions in the presence of 3.0 equivalents of BHT showed complete inhibition of product **3a** (Scheme 7A). This experiment suggested that the reaction is proceeding *via* the radical pathway. To showcase the synthetic utility, the scale-up 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 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 ^{1}H NMR, ^{13}C NMR, HRMS, and XRD, are given in the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The research work was supported by SERB (CRG/2022/008887) and IoE/2021/12/FRP for funding and USIC for instrumentation facilities. S. A. M. and D. T. are thankful to CSIR for their fellowship. The authors thank Mr Sanjay Kumar for the SC-XRD data and Mr Wasim Mukadam for the urgent supply of chemicals.

Notes and references

1 (*a*) M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weiberth, *Green Chem.*, 2018, **20**, 5082–5103; (*b*) N. Kerru, S. V. H. S. Bhaskaruni, L. Gummidi, S. N. Maddila, S. Maddila and S. B. Jonnalagadda, *Synth. Commun.*, 2019, **49**, 2437–2459; (*c*) N. Kerru, L. Gummidi, S. N. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Inorg. Chem. Commun.*, 2020, **116**, 107935; (*d*) N. Kerru, S. V. H. S. Bhaskaruni, L. Gummidi, S. N. Maddila, S. Maddila, S. RaRana, P. Singh and S. B. Jonnalagadda, *Appl. Organomet. Chem.*, 2019, **33**, e4722.

2 (*a*) P. S. V. Kumar, L. Suresh, G. Bhargavi, S. Basavoju and G. V. P. Chandramouli, *ACS Sustainable Chem. Eng.*, 2015, **3**, 2944–2950; (*b*) N. Isambert, M. M. S. Duque, J. C. Plaquevent, Y. Genisson, J. Rodriguez and T. Constantieux, *Chem. Soc. Rev.*, 2011, **40**, 1347–1357; (*c*) T. Itoh, *Chem. Rev.*, 2017, **117**, 10567–10607.

3 R. H. Vekariya and H. D. Patel, *RSC Adv.*, 2015, **5**, 49006–49030.

4 (*a*) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64–82; (*b*) Z. N. Siddiqui and T. Khan, *Tetrahedron Lett.*, 2013, **54**, 3759–3764; (*c*) M. V. Reddy, J. S. Kim, K. T. Lim and Y. T. Jeong, *Tetrahedron Lett.*, 2014, **55**, 6459–6462.

5 (*a*) V. Declerck, E. Colacino, X. Bantreil, J. Martinez and F. Lamaty, *Chem. Commun.*, 2012, **48**, 11778–11780; (*b*) W. J. Zhou, K. H. Wang and J. X. Wang, *J. Org. Chem.*, 2009, **74**, 5599–5602; (*c*) S. Chandrasekhar, C. Narsihmulu, S. S. Sultana and N. R. Reddy, *Org. Lett.*, 2002, **4**, 4399–4401.

6 K. S. Feu, A. F. de la Torre, S. Silva, M. A. F. de Moraes Junior, A. G. Correa and M. W. Paixao, *Green Chem.*, 2014, **16**, 3169–3174.

7 S. Chandrasekhar, V. Patro, L. N. Chavan, R. Chegondi and R. Gree, *Tetrahedron Lett.*, 2014, **55**, 5932–5935.

8 M. H. Ghom, M. S. Naykode, V. T. Humne and P. D. Lokhande, *Tetrahedron Lett.*, 2019, **60**, 1029–1031.

9 (*a*) R. Mallepalli, D. K. R. Vennam and R. S. Perali, *Tetrahedron Lett.*, 2016, **57**, 4541–4543; (*b*) X. Zhong, G. Dou and D. Wang, *Molecules*, 2013, **18**, 13139–13147.

10 J. Wang, L. He, C. Miao and J. Gao, *ChemSusChem*, 2009, **2**, 755–760.

11 (*a*) P. Aeberli, J. H. Gogerty, W. J. Houlihan and L. C. Iorio, *J. Med. Chem.*, 1976, **19**, 436–438; (*b*) R. Correa, V. C. Filho, P. W. Rosa, C. L. Pereira, V. Schlemper and R. J. Nunes, *Pharm. Pharmacol. Commun.*, 1997, **3**, 67–71; (*c*) I. H. Hall, O. T. Wong and J. P. Scovill, *Biomed. Pharmacother.*, 1995, **49**, 251–258; (*d*) A. M. Crider, T. M. Kolczynski and K. M. Yates, *J. Med. Chem.*, 1980, **23**, 324–326; (*e*) D. H. Rich and J. H. Gardner, *Tetrahedron Lett.*, 1983, **24**, 5305–5308; (*f*) G. J. Kaczorowski, O. B. McManus, B. T. Priest and M. L. Garcia, *J. Gen. Physiol.*, 2008, **131**, 399–405; (*g*) V. C. Filho, R. J. Nunes, J. B. Calixto and R. A. Yunes, *Pharm. Pharmacol. Commun.*, 1995, **1**, 399–401; (*h*) T. P. Johnston, J. R. Piper and C. R. Stringfellow, *J. Med. Chem.*, 1971, **14**, 350–354; (*i*) D. L. Musso, F. R. Cochran, J. L. Kelley, E. W. McLean, J. L. Selph and G. C. Rigdon, *J. Med. Chem.*, 2003, **46**, 399–408; (*j*) F. C. Pennington, P. A. Guercio and I. A. Solomons, *J. Am. Chem. Soc.*, 1953, **75**, 2261; (*k*) F. Zentz, A. Valla, R. L. Guillou, R. Labia, A.-G. Mathot and D. Sirot, *Farmaco*, 2002, **57**, 421–426; (*l*) B. G. Hazra, V. S. Pore, S. Dey, S. Datta, M. P. Darokar, D. Saikia, S. P. S. Khanuja and A. P. Thakur, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 773–777; (*m*) M. J. Kornet, A. M. Crider and E. O. Magarian, *J. Med. Chem.*, 1977, **20**, 405–409; (*n*) M. Isaka, W. Prathumpai, P. Wongsa and M. Tanticharoen, *Org. Lett.*, 2006, **8**, 2815–2817.

12 W. Löscher and D. Schmidt, *Epilepsia*, 2011, **52**, 657–678.

13 (*a*) K. Luo, Y. Bao, F. Liu, C. Xiao, K. Li, C. Zhang, R. Huang, J. Lin, J. Zhang and Y. Jin, *Eur. J. Med. Chem.*, 2019, **179**, 805–827; (*b*) K. Kamiński, S. Rzepka and J. Obniska, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5800–5803; (*c*) H. Kim, S. Cho, M. Yoo, S. Kang, K. Kim, H. Lee, J. Song, S. Rhee, W. Jung, J. Ahn, J. Jung and K. Jung, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 5213–5220.

14 W. Fan, L. Xing, N. Chen, X. Zhou, Y. Yu and S. Liu, *J. Phys. Chem. B*, 2019, **123**, 8057–8064.

15 (*a*) E. M. Mucker, A. J. Goff, J. D. Shamblin, D. W. Grosenbach, I. K. Damon, J. M. Mehal, R. C. Holman, D. Carroll, N. Gallardo, V. A. Olson, C. J. Clemmons, P. Hudson and D. E. Hruby, *Antimicrob. Agents Chemother.*, 2013, **57**, 6246–6253; (*b*) S. M. Hoy, *Drugs*, 2018, **78**, 1377–1382; (*c*) D. W. Grosenbach, K. Honeychurch, E. A. Rose, J. Chinsangaram, A. Frimm, B. Maiti, C. Lovejoy, I. Meara, P. Long and D. E. Hruby, *N. Engl. J. Med.*, 2018, **379**, 44–53.

16 (*a*) Q. Lin, Y. Zhang, Z. Fu, B. Hu, Z. Si, Y. Zhao, H. Shi and D. Cheng, *Med. Chem.*, 2010, **28**, 115577; (*b*) M. Kudo, M. Morimoto, M. Moriguchi, N. Izumi, T. Takayama, H. Yoshiji, K. Hino, T. Oikawa, T. Chiba, K. Motomura, J. Kato, K. Yasuchika, A. Ido, T. Sato, D. Nakashima, K. Ueshima, M. Ikeda, T. Okusaka, K. Tamura and J. Furuse, *Cancer Sci.*, 2020, **111**, 3759–3769.

17 (*a*) M. Ochiai, M. Inenaga, Y. Nagao, R. M. Moriarty, R. K. Vaid and M. P. Duncan, *Tetrahedron Lett.*, 1988, **29**, 6917–6920; (*b*) Y. M. Hijji and E. Benjamin, *Heterocycles*, 2006, **68**, 2259–2267; (*c*) E. Benjamin and Y. Hijji, *Molecules*, 2008, **13**, 157–169; (*d*) J. Deng, Q. G. Zhang, T. Pan, Q. Xu, Q. X. Guo and Y. Fu, *RSC Adv.*, 2014, **4**, 27541–27544.

18 (*a*) L. Zhang, Z. Li and Z. Q. Liu, *Org. Lett.*, 2014, **16**, 3688–3691; (*b*) L. Zheng, Z. Z. Zhou, Y. T. He, L. H. Li, J. W. Ma, Y. F. Qiu, P. X. Zhou, X. Y. Liu, P. F. Xu and Y. M. Liang, *J. Org. Chem.*, 2016, **81**, 66–76; (*c*) X. H. Hao, P. Gao, X. R. Song, Y. F. Qiu, D. P. Jin, X. Y. Liu and Y. Liang, *Chem. Commun.*, 2015, **51**, 6839–6842; (*d*) M. R. Mutra, V. S. Kudale, J. Li, W. H. Tsai and J. J. Wang, *Green Chem.*, 2020, **22**, 2288–2300; (*e*) M. R. Mutra, J. Li, Y. T. Chen and J. J. Wang, *Chem.–Eur. J.*, 2022, **28**, e202200742.

19 (*a*) X. F. Xia, W. He, G. W. Zhan and D. Wang, *Org. Chem. Front.*, 2019, **6**, 342–346; (*b*) Y. Liu, J. L. Zhang, R. J. Song, P. C. Qian and J. H. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 9017–9020; (*c*) Z. J. Shen, Y. N. Wu, C. L. He, L. He, W. J. Hao, A. F. Wang, S. J. Tu and B. Jiang, *Chem. Commun.*, 2018, **54**, 445–448; (*d*) J. K. Qiu, B. Jiang, Y. L. Zhu, W. J. Hao, D. C. Wang, J. Sun, P. Wei, S. J. Tu and G. Li, *J. Am. Chem. Soc.*, 2015, **137**, 8928–8931.

20 (*a*) Y. Wang, Y. Zhao, C. Cai, L. Wang and H. Gong, *Org. Lett.*, 2021, **23**, 8296–8301; (*b*) L. Navarro, G. Rosell, S. Sánchez, N. Boixareu, K. Pors, R. Pouplana, J. M. Campanera and M. D. Pujol, *Bioorg. Med. Chem.*, 2018, **26**, 4113–4126; (*c*) H. Zhang, J. Collins, R. Nyamwihura, S. Ware, M. Kaiser and I. V. Ogungbe, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 1647–1651; (*d*) F. Reck, F. Zhou, M. Girardot, G. Kern, C. J. Eyermann, N. J. Hales, R. R. Ramsay and M. B. Gravestock, *J. Med. Chem.*, 2005, **48**, 499–506.

21 (*a*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369; (*b*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2013, **114**, 2432–2506; (*c*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359; (*d*) D. Cahard and V. Bizet, *Chem. Soc. Rev.*, 2014, **43**, 135–147.

22 (*a*) F. Hou, Y. Ning, L. Song, Z. Tan, J. Yang, Z. Liu and F. E. Chen, *Org. Lett.*, 2023, **25**, 7810–7815; (*b*) X.-X. Meng, Q.-Q. Kang, J.-Y. Zhang, Q. Li, W.-T. Wei and W.-M. He, *Green Chem.*, 2020, **22**, 1388–1392.

23 (*a*) A. K. Mourad, J. Leutzow and C. Czekelius, *Angew. Chem., Int. Ed.*, 2012, **51**, 11149–11152; (*b*) K. Tanaka, T. Osaka, K. Noguchi and M. Hirano, *Org. Lett.*, 2007, **9**, 1307–1310; (*c*) M. R. Mutra, Y. Chen and J. Wang, *Adv. Synth. Catal.*, 2023, **365**, 1012–1019.

24 (*a*) M. R. Mutra, J. Li and J.-J. Wang, *Chem. Commun.*, 2023, **59**, 6584–6587; (*b*) M. R. Mutra and J.-J. Wang, *Nat. Commun.*, 2022, **13**, 2345.

25 S. A. Meena, P. Sharma and A. K. Verma, *Chem. Commun.*, 2023, **59**, 7271–7274.

26 Y. Guo, H. Liao, M. Pan, C. Zhao, Y. Qian, X. Liu and L. Rong, *J. Org. Chem.*, 2024, **89**, 3857–3867.

27 (*a*) R. K. Saunthwal, K. M. Saini, N. Grimblat, A. K. Danodia, S. Kumar, V. Gandon and A. K. Verma, *Org. Lett.*, 2022, **24**, 5018–5022; (*b*) D. Thakur, T. Aggarwal, N. Muskan, N. Sushmita and A. K. Verma, *J. Org. Chem.*, 2023, **88**, 2474–2486; (*c*) Sushmita, T. Aggarwal, K. M. Saini and A. K. Verma, *Adv. Synth. Catal.*, 2021, **363**, 4555–4560; (*d*) S. Verma, M. Kumar and A. K. Verma, *Org. Lett.*, 2020, **22**, 130–134.

28 H. S. Lee, *J. Dent. Anesth. Pain Med.*, 2016, **16**, 237–244.

29 (*a*) Y.-L. Zhu, B. Jiang, W.-J. Hao, A.-F. Wang, J.-K. Qiu, P. Wei, D. -C Wang, G. Li and S.-J. Tu, *Chem. Commun.*, 2016, **52**, 1907–1910; (*b*) A. Tota, S. St John-Campbell, E. L. Briggs, G. O. Estévez, M. Afonso, L. Degennaro, R. Luisi and J. A. Bull, *Org. Lett.*, 2018, **20**, 2599–2602.