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Singlet-oxygen-driven stereoselective iodothiocyanation and iodoselenocyanation of alkynes

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We present here a series of low-energy visible-light-induced metal-free C–I, C–S, and C–Se cross-coupling reactions for the formation of iodo-vinyl-thiocyanates (IVTs) and iodo-vinyl-selenocyanates (IVSs) using alkynes, iodine and ammonium thiocyanate (NH_4SCN)/potassium selenocyanate (KSeCN) in the presence of oxygen at room temperature. Upon photo-irradiation, iodine, molecular oxygen, and NH_4SCN synergistically generate iodine radical, singlet oxygen ($^1O_2$), and $^{\bullet}SCN$/$^{\bullet}SeCN$ radicals, respectively, and selectively react with alkyne to form stereoselective *E*-configured IVTs and IVSs. Iodine plays a significant role as I_2 acts as a photoactive species, undergoing homolytic cleavage to form iodine radicals, while singlet oxygen is produced *via* energy transfer (ET), and thiocyanate/selenocyanate radicals *via* single-electron transfer (SET) process. Moreover, green chemistry metrics and Eco-Scale evaluations highlight that the current stereoselective oxidative C–I, C–S, and C–Se coupling protocol aligns well with sustainable principles, establishing it as a viable and environmentally benign approach to organic synthesis.

Sustainability spotlight

This study presents a sustainable, metal-free, and oxidant-free photochemical strategy for synthesizing iodo-vinyl-thiocyanates and iodo-vinyl-selenocyanates under mild, visible-light irradiation conditions. The dual role of iodine as both a reactant and a photocatalyst enables the *in situ* generation of iodine radicals and singlet oxygen ($^1O_2$) without the need for external catalysts or hazardous oxidants. This approach minimizes chemical waste, reduces energy consumption, and aligns with the principles of green chemistry by promoting safer reaction conditions and resource efficiency. Evaluation through green chemistry metrics (*E*-factor) and Eco-Scale further validates the environmental compatibility of this method. The resulting iodo-thiocyanates/-selenocyanates also offer valuable synthetic versatility, serving as useful intermediates for diverse organic transformations and functional group elaborations.

1 Introduction

The adoption of visible light to drive environmentally benign and cost-effective transformations while unlocking unique synthetic potential poses a substantial challenge in current synthetic strategies. In general, photoredox catalysis depends on the propensity of metal complexes and organic dyes to generate reactive radicals *via* single-electron processes under photo-irradiation.[1–4] Nevertheless, in certain instances, reactants simultaneously function as photocatalysts. This dual role holds profound implications in green chemistry, serving as a cornerstone of sustainable chemistry and advanced organic synthesis.[5–7] Thus, a low-energy, visible-light-induced, metal-free and photocatalyst-free process for cross-coupling reactions involving heteroatoms or halogens would be an exceptional discovery in synthetic organic chemistry.

Organic thiocyanates and selenocyanates are highly significant owing to their diverse applications in organic synthetic transformations, pharmaceuticals, and environmental chemistry.[8–12] Thiocyanates are widely used in catalysis,[13] anti-inflammatory and antimicrobial treatments,[14] and drug synthesis,[15] while selenocyanates are currently gaining interest for their strong antioxidant,[16] antileishmanial,[17] anticancer,[18] and electronic properties.[19] Their unique reactivity and biological roles[20,21] make them valuable compounds for ongoing research and practical use. Sulfur- and selenium-containing organic compounds are indispensable across diverse fields, from biochemistry and medicine to materials and environmental science.[22,23] In particular, iodothiocyanates and iodo-selenocyanates are important scaffolds in organic synthesis, incorporating more than one versatile functionality. Their structural significance establishes them as structural intermediates or precursors for synthesizing a wide range of multi-substituted alkenes, valuable heterocycles,[24,25] and other complex molecules.[26] Notably, *E*-configured iodo-vinyl-thiocyanates or iodo-vinyl-selenocyanates exhibit enhanced reactivity due to the presence of vinylic proton coupled with an electrophilic iodine center, facilitating diverse organic transformation including cross-coupling reactions and

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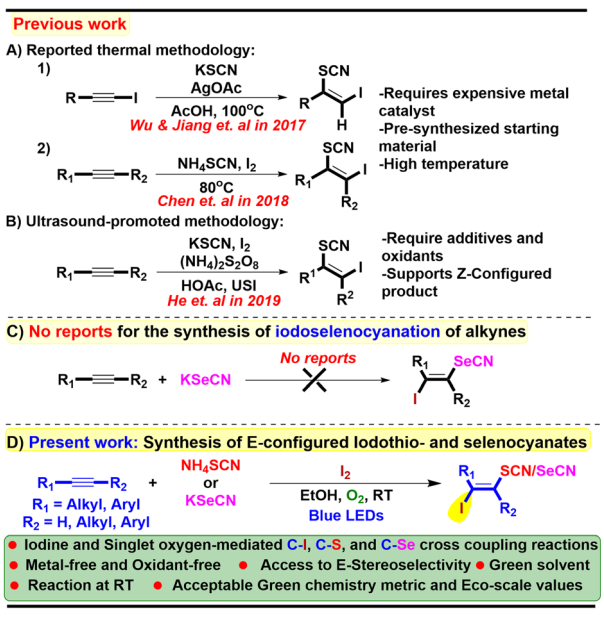
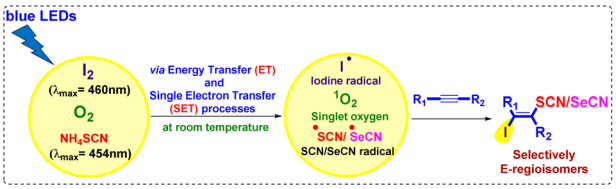
cyclizations.[27,28] Considering their usefulness, there is a necessity to develop a simple and green synthetic protocol (metal-free, oxidant-free, and photocatalyst-free) for the synthesis of iodo-vinyl-thiocyanates (IVTs) and iodo-vinyl-selenocyanates (IVSs).

The literature records include only a limited number of reports on the synthesis of iodo-vinyl-thiocyanates, specifically three, as illustrated in Scheme 1. In 2017, Wu and Jiang[29] proposed a synthetic approach for the preparation of (*Z*)-iodo vinyl thiocyanates *via* silver-catalyzed thiocyanation of (iodo-ethynyl)benzene (Scheme 1, A 1). However, a notable limitation lies in the necessity of pre-synthesizing 1-iodoalkynes from corresponding terminal alkynes through a cumbersome two-step procedure.[30] Later, Chen *et al.*[31] attempted to promote the synthesis of β-iodo vinylthiocyanates from alkynes at 80 °C (Scheme 1, A 2). Subsequently, He *et al.*[32] reported a novel ultrasound-assisted β-iodo vinylthiocyanation reaction from alkynes, iodine, potassium thiocyanate and ammonium persulfate ($(NH_4)_2S_2O_8$) (a strong oxidant) (Scheme 1, B). Nonetheless, no studies have reported on the synthesis of iodo-vinyl-selenocyanates (Scheme 1, C). Despite all the above mentioned excellent advances, these protocols still have some limitations, such as (a) the use of an expensive metal catalyst; (b) harsh reaction conditions; (c) the requirement of a pre-synthesized starting material (iodoalkynes); (d) the use of non-disposable and excess amounts of strong oxidants; (d) the requirement of specialized equipment; and (e) the generation of large amounts of chemical waste (leading to higher *E*-factors), lowering the reaction mass efficiency (RME) and atom efficiency. Thus, these methods are economically infeasible and add deleterious effects on the environment. To overcome the limitations associated with thermal reactions, visible light is a green and sustainable mode of activation for various chemical transformations.[33,34]



Scheme 1 Comparison of literature processes and the current photochemical process: (A) thermal methodology; (B) ultrasound-promoted methodology; (C) iodoselenocyanation of alkynes; (D) synthesis of *E*-configured iodothio- and selenocyanates.



Scheme 2 Iodine (I_2) and singlet oxygen ($^1O_2$)-mediated C–I, C–S, and C–Se cross-coupling reaction.

In this regard, no study has ever documented the visible-light-driven stereoselective iodothiocyanation of alkynes. Moreover, to mitigate chemical waste generation and environmental pollution, there is a need to develop a green photochemical and sustainable process that minimizes the formation of side products and chemical wastes. To this context, our group has reported various green methods for a variety of C–C, C–N, C–S, C–O oxidative cross-coupling, and C–H annulation reactions[35,53] by using visible light and the simple, inexpensive, earth-abundant CuCl as a catalyst. Herein, we report on metal-free and photocatalyst-free oxidative C–I, C–S, and C–Se cross-coupling reactions for the formation of iodo-vinyl-thiocyanates (IVTs) and iodo-vinyl-selenocyanates (IVSs) using alkynes, iodine and ammonium thiocyanate (NH_4SCN)/potassium selenocyanate (KSeCN) in the presence of oxygen under low energy visible light irradiation at room temperature (Scheme 1, D). Here, iodine plays an important role as it acts as a photochemical reagent, as well as a reactant. Upon photo-irradiation, iodine generates iodine radicals *via* homolytic cleavage of I_2, singlet oxygen *via* energy transfer (ET), and thiocyanate/selenocyanate radicals *via* single-electron transfer (SET) process (Scheme 2).

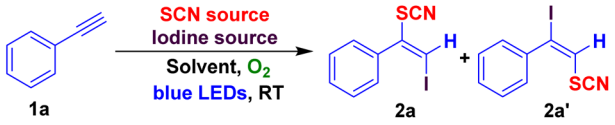
Moreover, upon photo-irradiation, molecular oxygen generates singlet oxygen, which ultimately generates SCN/SeCN radicals in the SET process and NH_4SCN generates $^1O_2$ *via* the ET process. Furthermore, these generated radicals selectively react with alkyne and stereoselectively form *E*-configured iodo-vinyl-thiocyanates (IVTs) and iodo-vinyl-selenocyanates (IVSs) (Scheme 2).

The overall significance of this green protocol includes the following: (a) a green and simple protocol for the oxidative C–I, C–S, and C–Se cross-coupling reaction for the formation of E-configured IVTs and IVSs at RT; (b) the versatile role of iodine as a photochemical reagent and a reactant; (c) first study to report the synthetic protocol for iodo-vinyl-selenocyanates; (d) green chemistry metrics and eco-scale evaluations indicate that the product formation is accompanied with a minimal amount of wastes (low *E*-factor) and with high reaction mass efficiency (RME).

2 Results and discussion

The optimization of reaction parameters for the photooxidative iodothiocyanation reaction of alkynes is outlined in Table 1. Herein, phenylacetylene, ammonium thiocyanate (SCN source), and molecular iodine (I source) were selected as the model substrates. First, the reaction of phenylacetylene with

Table 1 Optimization of the reaction conditions[a]



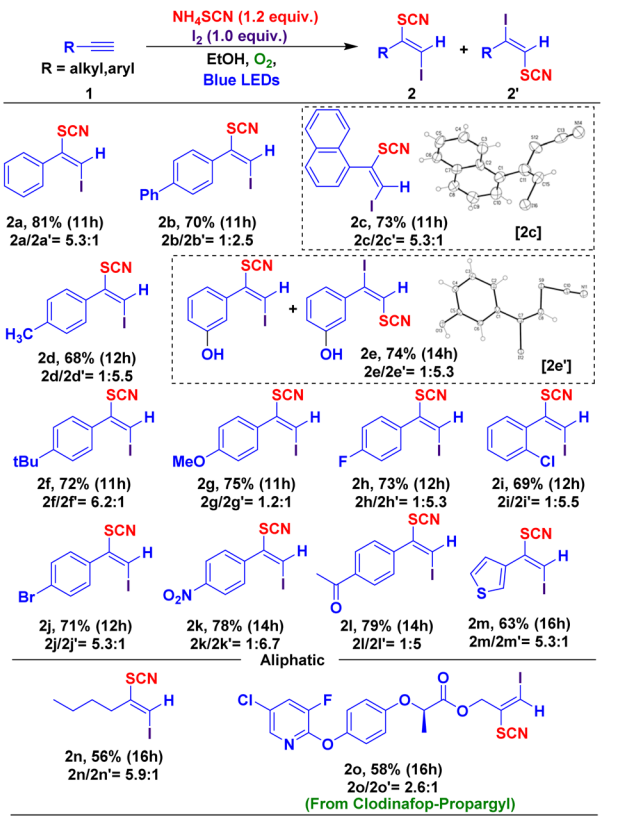
Entry	SCN source	Iodine source	Solvent	Yield (%)[b]	(2a : 2a′)[c]
1	NH_4SCN	I_2	CH_3CN	73	5.3 : 1
2	NH_4SCN	KI	CH_3CN	Trace	
3	NH_4SCN	NaI	CH_3CN	Trace	—
4	NaSCN	I_2	CH_3CN	47	5 : 1
5	KSCN	I_2	CH_3CN	52	2 : 1
6	NH_4SCN	I_2	DCM	26	5.3 : 1
7	**NH_4SCN**	**I_2**	**EtOH**	**81**	**5.3 : 1**
8	NH_4SCN	I_2	DMF	27	5.3 : 1
9	NH_4SCN	I_2	THF	39	5 : 3
10	NH_4SCN	I_2	H_2O	22	5.3 : 1
11[d]	NH_4SCN	I_2	EtOH	Trace	—
12[e]	NH_4SCN	I_2	EtOH	46	3.4 : 1
13[f]	NH_4SCN	I_2	EtOH	68	5.3 : 1
14[g]	NH_4SCN	I_2	EtOH	66	5.3 : 1
15[h]	NH_4SCN	I_2	EtOH	52	5.3 : 1

[a] Unless otherwise mentioned, the reaction condition is as follows; 1a (0.5 mmol), 1.2 equiv. of the SCN source, 1.0 equiv. of the iodine source, and solvent (3 mL). The mixture was irradiated with blue LEDs (power density: 150 mW cm^{-2} at 460 nm) for 11 h in an oxygen atmosphere (1 atm). [b] Yield of the isolated product. [c] Ratio of **2a**/**2a′** was estimated by the integral area of the vinyl hydrogen atom of the product. [d] The reaction was conducted in dark at RT. [e] In N_2 atmosphere; and. [f] In air. [g] Used 0.6 equiv. of the iodine source. [h] Used 0.5 equiv. of iodine source. n.r = No reaction.

ammonium thiocyanate (SCN source) and molecular iodine (I source) in the presence of oxygen (O_2) in acetonitrile (ACN) solvent under visible light irradiation for 11 h formed the inseparable regioisomers, (*E*)-(2-iodo-1-thiocyanatovinyl) benzene (**2a**) and (*E*)-(1-iodo-2-thiocyanatovinyl)benzene (**2a′**), in 73% yield with a ratio of 5.3 : 1 (entry 1, Table 1). To investigate the iodine source, potassium iodide (KI) and sodium iodide (NaI) were used in the reaction (instead of I_2) (entries 2 and 3), achieving the desired products in trace yields. Next, the use of alternative SCN sources such as NaSCN (sodium thiocyanate) and KSCN (potassium thiocyanate) formed the desired products **2a**/**2a′** in low yields of 47% and 52%, respectively (entries 4 and 5). Subsequently, employing NH_4SCN as the thiocyanate source and iodine as an iodine source, a comprehensive solvent screening was conducted with solvents such as dichloromethane (DCM), ethanol (EtOH), dimethylformamide (DMF), tetrahydrofuran (THF) and water (H_2O) (entries 6–10), among which ethanol formed the desired products (**2a**/**2a′**) in 81% yield and with a good selectivity ratio of **2a**:**2a′** = 5.3 : 1.

Ethanol is recognized as a green and sustainable solvent. When the reaction was performed in dark (entry 11), products were afforded only in trace amounts. To our surprise, the reaction performed in a nitrogen atmosphere (entry 12) also achieved the products **2a**/**2a′** with a yield of 46%. Thus, it indicates that the reaction proceeds through two different pathways (or mechanisms). Later, when the reaction was conducted in an air atmosphere, products **2a**/**2a′** were obtained with a moderate yield of 68% (entry 13). Moreover, products **2a**/**2a′** were obtained with a moderate yield of 66% and 52% when the reaction was conducted with 0.6 and 0.5 equivalent of iodine (instead of 1.0 equiv.), respectively. Thus, these optimization reactions show that NH_4SCN, I_2, and visible light are vital components for the formation of *E*-configured iodo-vinyl-thiocyanate (IVTs) products in a good yield.

Having the optimal reaction conditions in hand, we directed our efforts toward examining the substrate scope of terminal alkynes for this oxidative difunctionalization (iodo and thiocyanate) reaction (Scheme 3). First, electron-neutral terminal alkynes and those bearing more than one aromatic ring (such as 4-ethynyl-1,1′-biphenyl and 2-ethynylnaphthalene) formed the respective *E*-configured iodothiocyanates in good yields (**2a–2c**). In the case of the substrate 1b, 4-ethynyl-1,1′-biphenyl (**2b′**) (thiocyanate at terminal position) was formed as a major product. Next, the terminal alkynes with electron-donating substituents (such as –Me, –OH, and –OMe) worked efficiently and formed the terminal substituted thiocyanate products **2d′**, **2e′**, and **2g′** as the major products in good to moderate yields, while 1-(*tert*-butyl)-4-ethynylbenzene selectively formed (*E*)-1-(*tert*-butyl)-4-(2-iodo-1-thiocyanatovinyl)benzene (**2f**) as the major product. Furthermore, regardless of their positions on the phenyl rings (*-ortho*, *-meta*, *-para*), the halogen (–Br, –Cl, and –F) substituted aromatic terminal alkynes all were well tolerated by this green oxidative iodothiocyanation reaction and formed *E*-configured iodo thiocyanatovinyl benzene **2h–2j** in an average



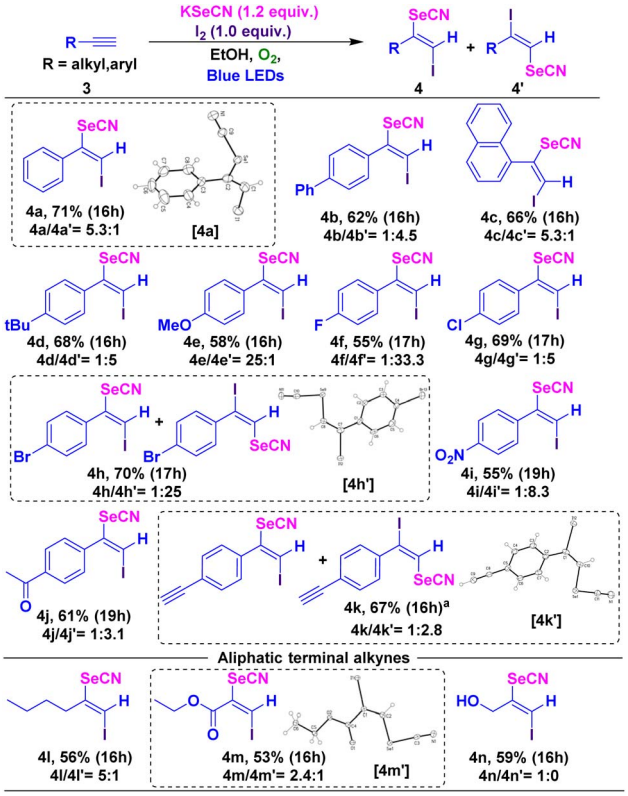
Scheme 3 Substrate scope of terminal alkynes for iodothiocyanation.

yield of 69–73%. Additionally, the terminal alkynes bearing electron-withdrawing groups, such as $-NO_2$ and $-COCH_3$, formed the vinyl-thiocyanates as the major products (**2k′**, **2l′**) in good yields.

Later, the heteroaryl terminal acetylene, 3-ethynylthiophene (**1m**) formed (*E*)-3-(2-iodo-1-thiocyanatovinyl)thiophene (**2m**) with a moderate yield of 63%. In contrast, ethynylpyridine did not undergo an oxidative iodothiocyanation reaction. This observation is consistent with our previous findings that the ethynylpyridines are inert for the photo–oxidation reaction. We observed that the pyridine-containing alkynes or internal alkynes could not undergo photo–oxidation reaction.[44,52,54–57] Moreover, an aliphatic terminal alkyne such as 1-hexyne formed the desired *E*-configured iodothiocyanate products **2n**/**2n′** with an average yield of 56%. Importantly, clodinafop–propargyl, a widely used herbicide, was well tolerated by this green photo-oxidative difunctionalization reaction and formed (*E*)-3-iodo-2-thiocyanatoallyl (*R*)-2-(4-((5-chloro-3-fluoropyridin-2-yl)oxy) phenoxy)propanoate (**2o**) as a major product. The structures of products **2c** (CCDC 2426651) and **2e′** (CCDC 2415478) were confirmed by single-crystal X-ray diffraction.[58]

To our delight, we discovered that the current metal-free, oxidative iodothiocyanation reaction conditions are effectively applicable to the iodoselenocyanation of alkynes. Only potassium selenocyanate (KSeCN) was used as a SeCN source, as other SeCN salts such as sodium selenocyanate (NaSeCN) and ammonium selenocyanate (NH_4SeCN) were not commercially available. The reaction conditions for the iodoselenocyanation of alkynes are as follows: 0.5 mmol alkyne (1), iodine (1.0 equiv.), and KSeCN (1.2 equiv.) in 3 mL of ethanol solvent. The reaction mixture was irradiated with blue LEDs (power density: 150 mW cm^{-2} at 460 nm) for 11 h in an oxygen atmosphere (1 atm). Using standard reaction conditions, we explored the substrate scope of the terminal alkynes presented in Scheme 4. Terminal alkynes bearing electron-neutral, electron-donating, halogen, and electron-withdrawing functional groups produced iodo-selenocyanate products **4**/**4′** as an inseparable mixture of regio-isomers in good yield (**4a–4m**). 4-Ethynyl-1,1′-biphenyl and 1-(*tert*-butyl)-4-ethynylbenzene formed **4b′** and **4d′**, respectively, (with SeCN at the terminal position) as a major product, whereas, the –OMe substituted terminal alkyne **3e** produced (*E*)-1-(2-iodo-1-selenocyanatovinyl)-4-methoxybenzene (**4e**) as the major product.

Subsequently, alkynes bearing halogen substituents and electron-withdrawing functional groups predominantly formed the iodoselenocyanate-functionalized products **4f′**, **4g′**, **4h′**, **4i′**, and **4j′** as the major product. Moreover, when the reaction of the diethynyl benzene substrate (**3k**) was performed with 2.0 equivalents of iodine and 2.4 equivalents of KSeCN, only mono-ethynyl iodoselenocyanate-functionalized products **4k**/**4k′** were obtained in 67% yield with (*E*)-1-ethynyl-4-(1-iodo-2-selenocyanatovinyl)benzene (**4k′**) as a major product. We did not observe any di-ethynyl iodoselenocyanate-functionalized products. Moreover, the present oxidative photochemical protocol worked well with aliphatic terminal alkynes, such as 1-hexyne, ethyl propiolate, and prop-2-yn-1-ol, and formed the corresponding iodoselenocyanate products **4l–4n** with high stereoselectivity. The structures of products **4a** (CCDC 2415348),



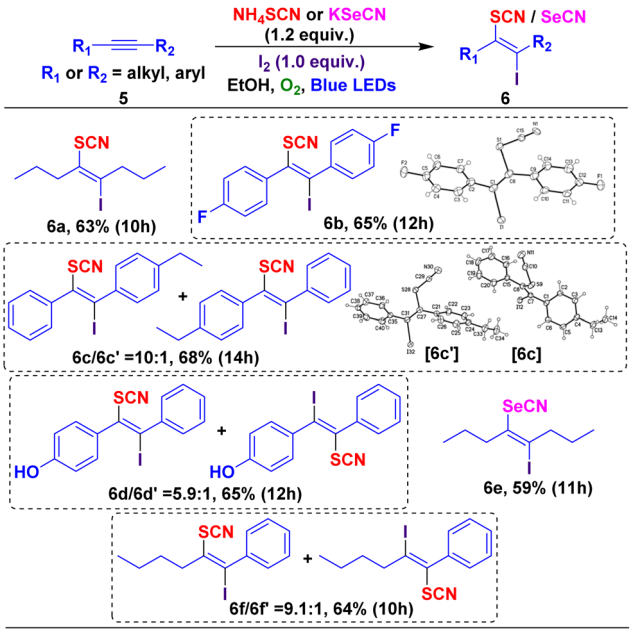
Scheme 4 Substrate scope of the terminal alkynes for iodo-selenocyanation. [a]Used 2.0 equivalents of iodine and 2.4 equivalents of KSeCN.

4h′ (CCDC 2415349), **4k′** (CCDC 2415484), and **4m′** (CCDC 2415490) were confirmed by single-crystal X-ray diffraction.[58]

Next, we investigated the substrate scope of symmetrical and unsymmetrical internal alkynes for iodothiocyanation and iodoselenocyanation reactions (Scheme 5). The symmetrical internal alkynes such as oct-4-yne, 1,2-bis(4-fluorophenyl) ethyne) worked well under standard reaction conditions and resulted in (*E*)-4-iodo-5-thiocyanatooct-4-ene (**6a**) and (*E*)-4,4′-(1-iodo-2-thiocyanatoethene-1,2-diyl)bis (fluorobenzene) (**6b**) in good yield, respectively. The unsymmetrical internal alkynes 1-ethyl-4-(phenylethynyl) benzene **5c** and 4-(phenylethynyl) phenol **5d** formed products **6c**/**6c′** and **6d**/**6d′** as inseparable regioisomers in good yield, respectively.

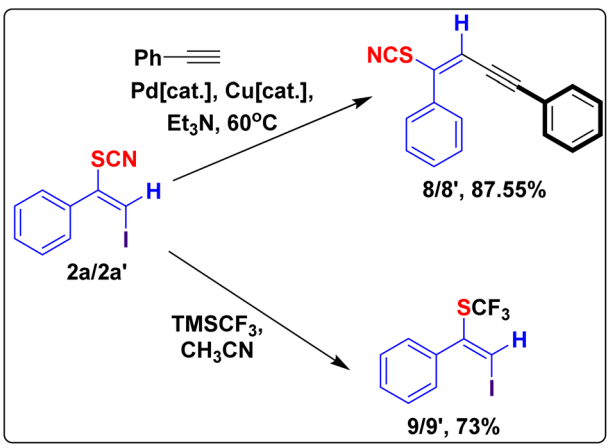
Similarly, an aliphatic internal alkyne such as oct-4-yne readily undergoes the photochemical oxidative iodo-selenocyanation reaction and forms (*E*)-4-iodo-5-selenocyanatooct-4-ene (**6e**) in 59% yield. Unfortunately, diaryl alkynes did not undergo the current photochemical oxidative iodoselenocyanation reaction. The reason for these unsuccessful substrates is not clear. Moreover, alky aryl internal alkynes such as hex-1-yn-1-ylbenzene (**5f**) readily formed products **6f**/**6f′** in 64% yield. The structures of **6b** (CCDC 2415489) and **6c**, **6c′** (CCDC 2415491) were confirmed by single-crystal X-ray diffraction.[58]

To demonstrate the utility of the *E*-configured organic iodo-vinyl-thiocyanate (IVT) products, we performed some synthetic

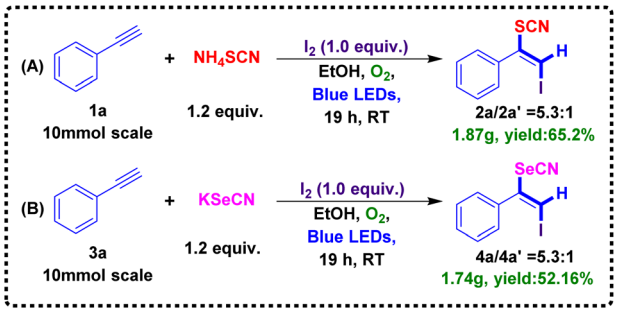


Scheme 5 Substrate scope of the terminal alkynes for internal alkynes.

modification reactions of products **2a**/**2a**′ as presented in Scheme 6. Given that iodine substituents serve as highly effective handles for palladium-catalyzed cross-coupling reactions, we carried out the Sonogashira cross-coupling reaction of (*E*)-(2-iodo-1-thiocyanatovinyl)benzene (**2a**/**2a**′) with phenylacetylene and afforded the product(*E*)-(1-thiocyanatobut-1-en-3-yne-1,4-diyl)dibenzene (**7**/**7**′) in 87% yield. Next, the thiocyanate functionality of (*E*)-(2-iodo-1-thiocyanatovinyl)benzene (**2a**/**2a**′) readily underwent trifluoromethylation, leading to the formation of (*E*)-(2-iodo-1-phenylvinyl)(trifluoromethyl)sulfane (**8**/**8**′). Thus, these facile transformations of iodo-vinyl-thiocyanate products (bearing two versatile functionalities, thiocyanate and iodine) exhibit the significance of the current photochemical oxidative C–I and C–S cross-coupling reactions in organic synthetic chemistry.



Scheme 6 Late-stage functionalization of **2a**/**2a**′.



Scheme 7 Gram-scale synthesis of: (A) (*E*)-(2-iodo-1-thiocyanatovinyl) benzene (**2a**); and (B) (*E*)-(2-iodo-1-selenocyanatovinyl) benzene (**4a**).

Additionally, to check the efficiency of the current stereoselective oxidative difunctionalization reaction, a 10 mmol scale (a gram-scale) reaction was performed (Scheme 7). The reaction of phenylacetylene (**1a**) (1.02 g, 10.0 mmol) with ammonium thiocyanate (0.91 g, 12.0 mmol) and molecular iodine (2.53 g, 10 mmol) in the presence of 15 mL ethanol solvent and O_2 (1 atm) under blue LEDs irradiation at room temperature for 19 h formed (*E*)-(2-iodo-1-thiocyanatovinyl) benzene products (**2a**) in 65.2% yield (1.87 g), along with the regio-isomer (*E*)-(1-iodo-2-thiocyanatovinyl)benzene (**2a**′). Following similar reaction conditions and using potassium selenocyanate (1.74 g, 12.0 mmol) as the selenocyanate source, we obtained the (*E*)-(2-iodo-1-selenocyanatovinyl) benzene product (**4a**) in 52.16% yield (1.74 g), together with the regio-isomer **4a**′. Furthermore, we evaluated the green chemistry metrics[50–53] for the current visible-light-driven difunctionalization reaction on a preparative scale for the synthesis of **2a** (Table 2) and **4a** (detailed evaluations shown in Table S1 in the SI). Among the various parameters of green chemistry metrics, the *E*-factor (environmental impact factor) is a crucial parameter of the green chemistry metrics as it denotes the total amount of waste generated in a reaction. The *E*-factor values for the synthesis of (*E*)-(2-iodo-1-thiocyanatovinyl) benzene (**2a**) and (*E*)-(2-iodo-1-selenocyanatovinyl)benzene (**4a**) are 3.24 and 4.61, respectively. Moreover, the literature lacks any reported photochemical approach for synthesizing **2a**, while the literature-reported thermal methodologies exclusively form the *Z*-configured iodo-vinyl-thiocyanates.

Next, we evaluated the eco-scale[50–53] value for the synthesis of (*E*)-(2-iodo-1-thiocyanatovinyl) benzene (**2a**) (Table 3) and (*E*)-(2-iodo-1-selenocyanatovinyl)benzene (**4a**) (see SI, Table S2). The eco-scale values for the current green photochemical method for the synthesis of **2a** and **4a** are 64.6 and 58.08 on a scale of 100, respectively. These values indicate that the current oxidative green photochemical method is an acceptable green protocol for the formation of stereoselective iodo-thiocyanation and iodo-selenocyanation products from a safety, economic, and ecological features point of view. In addition to these numeric evaluations of green chemistry metrics, the current photochemical oxidative C–I, C–S, and C–Se coupling method does not require harsh reaction conditions, metal catalysts, exogenous ligands, external photosensitizers, or additives.

Table 2 Evaluation of the green chemistry metrics for the synthesis of 2a

$$\text{Atom economy (\%) (AE)} = \frac{\text{Molecular mass of desired product}}{\text{Molecular mass of all reactants}} \times 100$$

$$\text{Reaction mass efficiency (\%) (RME)} = \frac{\text{Mass of desired product}}{\text{Mass of all reactants}} \times 100$$

Reactant 1	Phenylacetylene	1.02g	10.0 mmol	FW 102.13
Reactant 2	NH_4SCN	0.91g	12.0 mmol	FW 76.11
Reactant 3	I_2	2.53g	10.0 mmol	FW 253.81
Solvent	EtOH (15mL)	11.83g	----	----
Auxiliary	----	----	----	----
Recycled Solvent	EtOH (9.3mL)	7.34g	----	----
Product	(*E*)-(2-iodo-1-thiocyanatovinyl)benzene 2a/2a' = 5.3:1	1.87g	6.51 mmol	FW 287.12

Product yield = 65.2%

$$\text{E-factor} = \frac{1.02 + 0.91 + 2.53 + 11.83 - (7.34+1.87)}{1.87g} = 3.24 \text{ Kg waste/1 Kg of product}$$

$$\text{Atom economy} = \frac{287.12}{305.14} \times 100 = 94.09\%$$

$$\text{Atom efficiency} = 65.2\% \times 94.09\% / 100 = 61.35\%$$

$$\text{Carbon efficiency} = \frac{9}{8+1} \times 100 = 100\%$$

$$\text{Reaction mass efficiency} = \frac{1.87g}{1.02g+0.91g+2.53g} \times 100 = 41.92\%$$

Table 3 Eco-scale calculation for the synthesis of 2a.

EcoScale = 100 - Sum of individual penalties

Score on EcoScale: >75, Excellent; >50, Acceptable; <50, Inadequate

A) Calculation of penalty points:

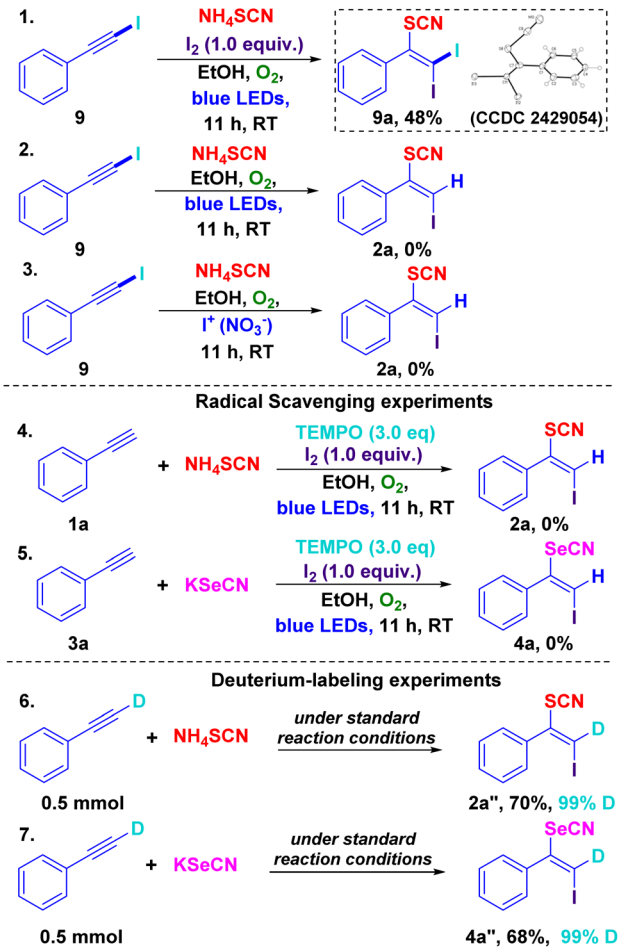
Parameters		Penalty points
1. Yield	(100-%yield)/2 = (100-65.2)/2 = 17.4	17.4
2. Price of reaction components (To obtain 10 mmol of end product)		
a. Phenylacetylene	= 1.02g = $0.82	
b. NH_4SCN	= 0.91g = $0.07	
c. Iodine	= 2.53g = $0.17	
d. Ethanol	= 15mL = $0.01	
	Total price (USD) = $1.07	
	Thus, expensive (> $10 and < $50)	0
3. Safety		
Solvent : Ethanol		
Highly flammable (F)		5
4. Technical Setup		
Unconventional activation technique (Photochemical activation)		2
5. Temperature and time		
Room temperature and <24h		1
6. Workup and purification		
Removal of solvent with bp <150°C		0
Classical Chromatography		10
Total Penalty Points		35.4

B) EcoScale calculation:

EcoScale = 100- 35.4 = 64.6 (an acceptable synthesis)

2.1 Mechanistic studies

A series of control experiments were conducted to help elucidate the mechanistic pathway of the current green photochemical stereoselective oxidative difunctionalization reaction (Scheme 8). First, when the reaction of (iodoethynyl)benzene with ammonium thiocyanate and molecular iodine was conducted under standard reaction conditions for 11 h, 2,2-diiodo-1-thiocyanatovinyl)benzene product **9a** was obtained in 48% yield (eqn (1), Scheme 8). In contrast, when the reaction was performed in the absence of molecular iodine, the desired product **2a** was not obtained (eqn (2), Scheme 8). This observation indicates that molecular iodine plays a crucial role in the reaction. To examine whether the iodonium cation was involved in the formation of **2a**, iodonium nitrate was added to the reaction mixture at RT in dark for 11 h. However, no formation of **2a** was observed (eqn (3), Scheme 8), suggesting that the iodonium cation was not involved in the formation of **2a.** Next, the products (*E*)-(2-iodo-1-thiocyanatovinyl) benzene (**2a**/**2a′**) and (*E*)-(2-iodo-1-selenocyanatovinyl)benzene (**4a**/**4a′**) were not obtained when the current oxidative cross-coupling reactions were performed in the presence of the radical scavenger TEMPO ((2,2,6,6-tetramethylpiperidin-1yl)oxyl) under standard reaction conditions, confirming that the current oxidative coupling reactions are likely to proceed *via* a radical pathway (eqn (4) and



Scheme 8 Mechanistic investigations.

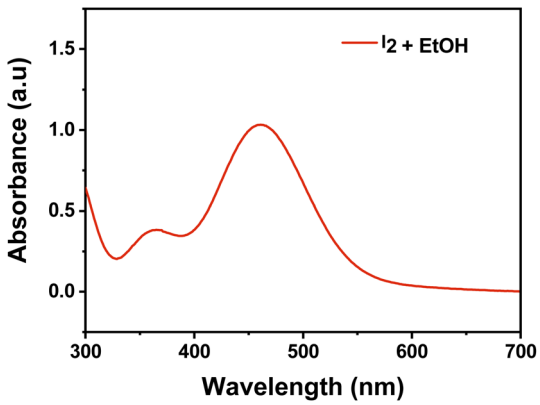


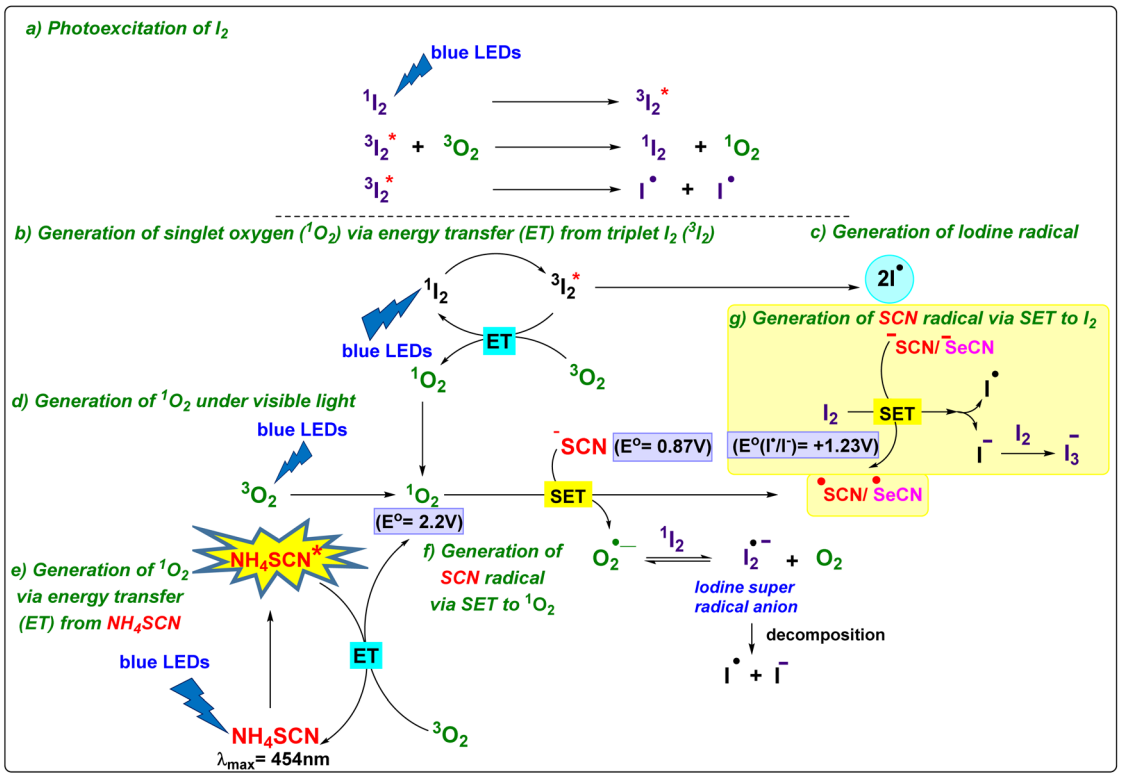
Fig. 1 UV-visible absorption spectra of I_2 in ethanol (EtOH).

(5), Scheme 8). Moreover, the EPR measurements of the reaction mixture show EPR signals corresponding to iodine radical ($I^{\bullet}$) and singlet oxygen ($^1O_2$) in the reaction mixture (see Fig. S1 in the SI).

Furthermore, we performed deuterium-labeling experiments for iodothiocyanation and iodoselenocyanation reactions under standard reaction conditions by using phenylacetylene-D1 as a substrate and obtained oxidative difunctionalized compounds **2a″** and **4a″** in 70% and 68% yields, respectively, with 99% of deuteration in both cases (eqn (6) and (7), Scheme 8) (see details in the SI). In addition, we presented the UV-visible absorption spectra of I_2 in ethanol (EtOH) in Fig. 1, which shows that I_2 has an absorbance at 460 nm.

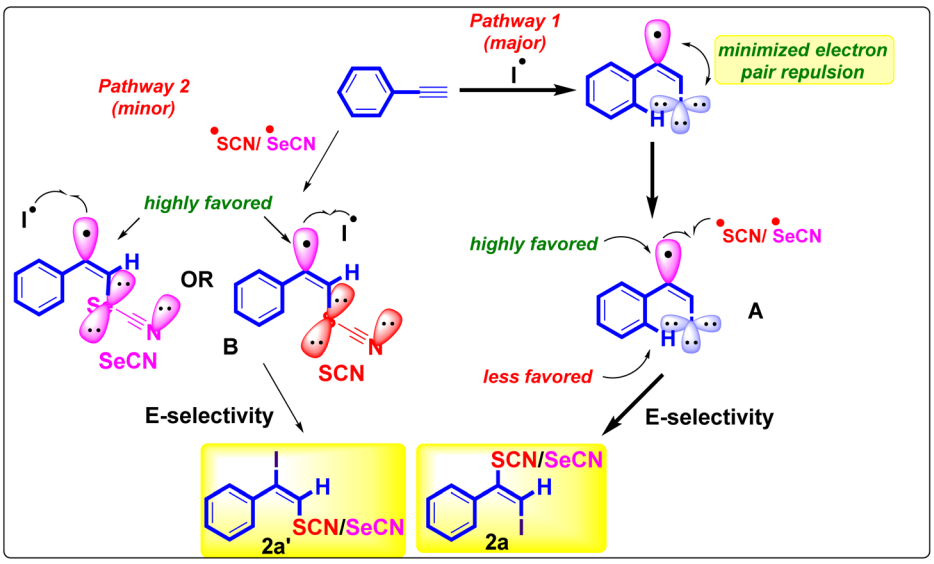
2.2 Mechanism

Based on our previous works,[35–54] the above presented mechanistic investigations and the UV-visible spectrum, a possible reaction mechanism for the current stereoselective oxidative difunctionalization reaction is proposed in Schemes 9 and 10. Scheme 9 shows various schematic representations for the generation of iodine radicals, singlet oxygen ($^1O_2$), and thiocyanate/selenocyanate ($^{\bullet}$SCN/$^{\bullet}$SeCN) radicals through multiple pathways. Scheme 10 presents the reaction mechanism for the reaction of $^{\bullet}$SCN/$^{\bullet}$SeCN and $^{\bullet}$I radicals with phenylacetylene (**1a**) to form selectively *E*-configured iodothiocyanate/iodo-selenocyanate products. First, upon photo-irradiation, (I_2, λ_{max} = 460 nm) molecular iodine generates the photoexcited triplet state iodine, which forms singlet oxygen ($^1O_2$) and molecular I_2 (ref. 59 and 60) upon energy transfer (ET) with O_2 (Scheme 9a and b). Moreover, the photoexcited triplet state iodine ($^3I_2$*) undergoes homolytic cleavage and generates two iodine radicals (Scheme 9c). Next, singlet oxygen ($^1O_2$) is also generated through the direct visible light photo-irradiation of molecular oxygen,[61] and *via* the energy transfer (ET) process from NH_4SCN to O_2 (ref. 54) (Scheme 9d and e). Furthermore, this generated singlet oxygen ($^1O_2$) (E° = +2.2 V_{NHE})[54–57] undergoes a single-electron transfer process (SET) by accepting an electron from thiocyanate anion (–SCN) (E° = +0.87 V_{NHE})[54–57] and simultaneously forms the $^{\bullet}$SCN radical and superoxide ($O_2^{\bullet-}$). This highly reactive superoxide further reacts with I_2 and forms molecular oxygen and iodine super radical anion ($I_2^{\bullet-}$), which



Scheme 9 Proposed mechanism: (a) photoexcitation of I_2; (b) generation of $^1O_2$ *via* ET from $^3I_2$; (c) generation of I$^\bullet$; (d) generation of $^1O_2$ under visible light; (e) generation of $^1O_2$ *via* ET from NH_4SCN; (f) generation of SCN$^\bullet$.

further decomposes and forms the iodine radical and iodide ion (Scheme 9f). Moreover, the thiocyanate (–SCN)/selenocyanate (–SeCN) (E° = +0.87 V_{NHE}) anion undergoes a single-electron transfer (SET) process by transferring an electron to I_2 (E° = +1.23 V_{NHE}),[62] which leads to the formation of the thiocyanate ($^\bullet$SCN)/selenocyanate ($^\bullet$SeCN) radicals, iodine radical and iodide ion. This iodide ion further reacts with I_2 to form I_3^-, which further reacts with singlet oxygen ($^1O_2$) and generates I_2 and iodine radicals (Scheme 9g). These $^\bullet$I and $^\bullet$SCN are readily added to the alkyne and form a carbon-centered radical intermediate A (Pathway 1) and B (Pathway 2), respectively (Scheme 10). The intermediate A formation pathway appears to dominate over the reaction intermediate B pathway under our standard reaction condition, presumably due to the generation of a larger quantity



Scheme 10 Proposed mechanism for the selective formation of the E-regioisomer of the iodo-vinyl-thiocyanates (IVTs) and iodo-vinyl-selenocyanates (IVSs).

of ˙I radical than the ˙SCN/˙SeCN radicals. The free radical on the intermediate A is located at the *trans*-position relative to the terminal iodine substituent due to the minimization of electron pair repulsion energy between the free radical electron and the three lone pair electrons on the terminal iodine substituent, which is similar to the valence shell electron pair repulsion (VSEPR) model for the explanation of the molecular geometry commonly described in General Chemistry textbooks. Subsequent coupling of the thiocyanate (˙SCN) or selenocyanate (˙SeCN) radicals to the free radical site at the *trans*-position leads to the formation of the desired stereoselective oxidative difunctionalized products. The current photochemical free-radical pathway for the stereoselective (*E*)-configured iodo-thiocyanation/iodo-selenocyanation of alkynes is different from the literature-reported thermal-driven iodonium-cation-mediated formation of (*Z*)-configured iodo-vinylthiocyanates.[29,31,32] In this mechanism, molecular iodine serves as a singlet oxygen photosensitizer/photochemical reagent and one of the reactants of the iodo-thiocyanation and -selenocyanation reaction, displaying its dynamic capability and unveiling extensive synthetic opportunities for advanced organic synthesis.

3 Conclusions

We report on the highly efficient, novel, practical yet simple photo-oxidative metal-free and photocatalyst-free C–I, C–S, and C–Se cross-coupling reactions for the stereoselective synthesis of (*E*)-configured iodo-vinyl-thiocyanates (IVTs) and iodo-vinyl-selenocyanates (IVSs). Iodine acts as a photoactive reactant and generates iodine radicals *via* homolytic cleavage of I_2, singlet oxygen *via* energy transfer (ET), and thiocyanate/selenocyanate radicals *via* single-electron transfer (SET) process. Moreover, the stereoselectivity occurs through a unique photochemical-driven iodine substituent-mediated *trans*-position (*E*)-configured radical–radical coupling process, which is in contrast to the literature-reported thermal-driven, iodonium-cation mediated *cis*-position (*Z*)-configured nucleophilic addition process. Overall, 35 examples are presented. Moreover, the IVTs and IVSs are applicable for the synthesis of valuable heterocycles and pharmaceutically active compounds. Green chemistry metric evaluations also show that the current photochemical process generates minimal amounts of waste with an *E*-factor of 3.24 and 4.61 for the synthesis of IVTs and IVSs, respectively. Furthermore, the eco-scale value signifies that this protocol is an acceptable green process from the safety, cost-efficient, and eco-conscious points of view.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2426651, 2415478, 2415348, 2415349, 2415484, 2415490, 2415489, 2415491 and 2429054 contain the supplementary crystallographic data for this paper.[58a–i]

Experimental details and characterization data are available in the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5su00867k.

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