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Photocatalyst/metal-free sequential C–N/C–S bond formation: Synthesis of *S*-arylisothioureas *via* photoinduced EDA complex activation

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ABSTRACT

A photocatalyst-free visible-light-promoted three-component reaction of thianthrenium salts, isothiocyanates, and amines is presented, which affords a rapid and efficient approach to *S*-arylisothioureas under mild conditions. This developed method exhibits the advantages of readily available raw materials, broad substrate scope, good functional tolerance, and operational simplicity. It is worth mentioning that the byproduct thianthrene can be recycled in quantity, ultimately maximizing the atomic economy of the reaction and avoiding chemical waste. Mechanism investigations support the strategy involving a photoinduced EDA complex.

Sulfur-containing compounds widely occur in natural products, and biologically active molecules. Therefore, seeking novel and efficient methods for the synthesis sulfur-containing skeletons has attracted the continuous attention of chemists [1-5]. Isothioureas are ubiquitous structural frameworks commonly found in natural products, agrochemicals, and pharmaceuticals [6]. In this structural family, *S*-arylisothioureas have also shown promising biological properties, such as anti-infective, antianginal and antiviral activities (Scheme 1a) [7,8]. In addition, isothiourea architectures are widely used as versatile synthons for natural products, bioactive molecules, herbicides, organocatalysts, and ligands [9]. In this respect, *S*-arylisothioureas are traditionally prepared by the reaction of arylthioureas with amines, benzensulfonic acid or alkyl halides [10,11]. Alternative method such as the reaction of aromatic thiols with benzotriazole-1-carboximidamides has also been developed [12]. Nevertheless, most of these methods still involve the use of toxic and unavailability of starting materials, harsh reaction conditions, and multi-step synthetic sequences. Therefore, the development of novel and efficient approach to *S*-arylisothioureas has received increased attention from biochemists and synthetic organic chemists. In 2014, Maes and co-workers reported a copper-catalyzed three-component reaction for the synthesis of *S*-aryl isothioureas starting from amines, isocyanides, and thiosulfonates (Scheme 1b) [13]. In 2017, Dong *et al.* developed an efficient copper-catalyzed *S*-arylation of thioureas leading to *S*-aryl isothioureas (Scheme 1c) [14,15]. Notably, very recently, Sun's group demonstrated an elegant approach to *S*-arylisothioureas from sulfoxides, isocyanides, and amines through a thermolysis-induced multicomponent tandem reaction (Scheme 1d) [16]. However, significant room still exists for improvement of these methods with regard to catalytic efficiency, generality, and reaction conditions.

Organothianthrenium salts are a significant class of sulfur-containing compounds, containing a neutral sulfur atom and a positively charged sulfur atom [17-19]. In 2019, Ritter *et al.* reported an elegant and convenient site-selective C–H thianthrenation of arenes leading to aryl thianthrenium salts [20]. Since this pioneering work, tremendous progress has been made using thianthrenium salts as the precursors for the construction of carbon–carbon and carbon–heteroatom bonds [21-31]. Notably, in 2023, Wang and co-workers also developed a novel copper-mediated thianthrenation of arylborons with thianthrene leading to thianthrenium salts [32]. Clearly, chemical conversions using thianthrenium salts as the aryl sources indirectly realizes the Csp^2-H bonds functionalization and arylboric acids activation. Therefore, the exploration of chemical transformations based on thianthrenium salts has important research value in the field of organic diversity synthesis.

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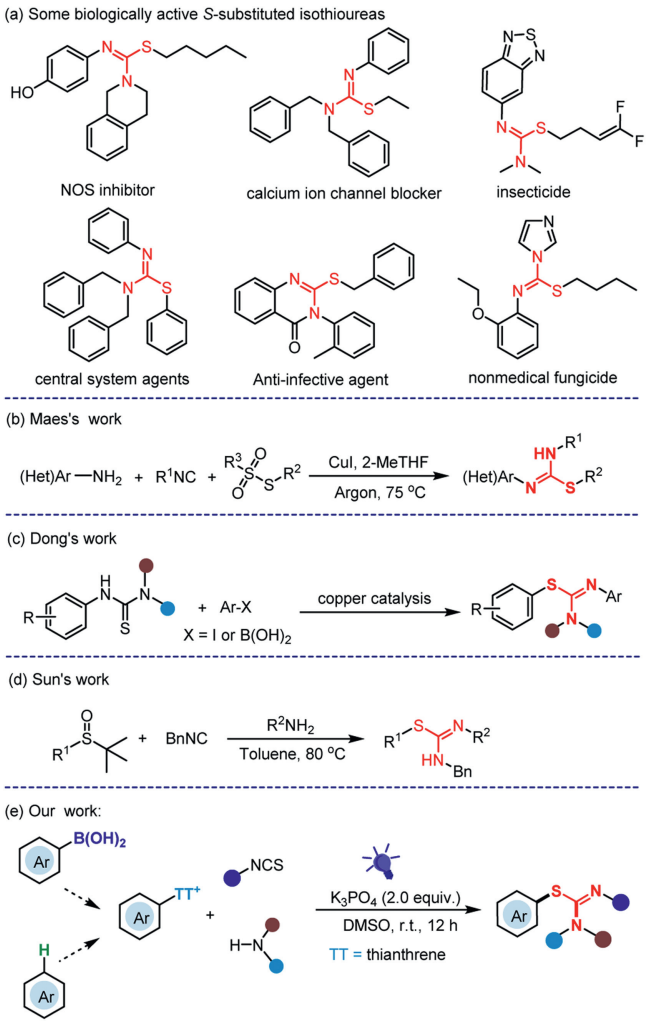
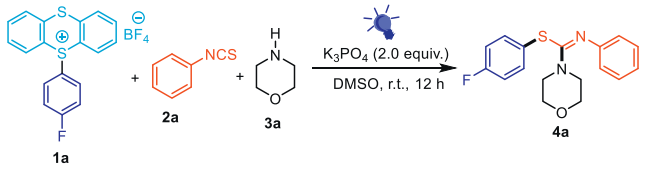


Scheme 1. Application and synthesis of isothioureas.

In recent years, visible-light-induced organic transformations has been recognized as a sustainable and promising strategy for organic transformations *via* photoinduced single electron transfer (SET) or energy transfer (EnT) processes [33-43]. In this area, the visible-light-accelerated of electron donor–acceptor (EDA) complexes have aroused on-going interest of chemists due to their easy operation and the unique ability of the complexes which can undergo a reversible inner-sphere SET process affording two high active radical species without additional any photoredox catalysts [44-46]. Very recently, a series of interesting studies on the photochemical conversion of thianthrenium salts based on EDA complex activation process have been developed [47-54]. However, the EDA strategy in this regard mainly focuses on the reactions between two molecules, developing the multicomponent EDA strategies based on thianthrenium salts is still in its infancy. In pursuit of step economy, the domino reaction has replaced multi-step chemical transformations which has a significant impact on the synthesis of fine chemicals and pharmaceutical intermediates [55-58]. Obviously, a quantum leap in efficiency could be achieved in a single synthesis operation using multicomponent EDA strategy. Since thianthrenium salts have been reported to act as radical acceptor in EDA complexes, we envisage that *S*-arylisothioureas could be synthesized indirectly starting from readily available arenes and arylboronic acids (Scheme 1e). As our continuing studies on photoredox catalysis [59-64], we herein report an efficient visible-light-induced multicomponent reaction for the synthesis of *S*-arylisothioureas from thianthrenium salts, isothiocyanates and secondary amines in the absence of transition metals or other photocatalysts (Scheme 1e).

Table 1
Screening for the optimal conditions.[a]

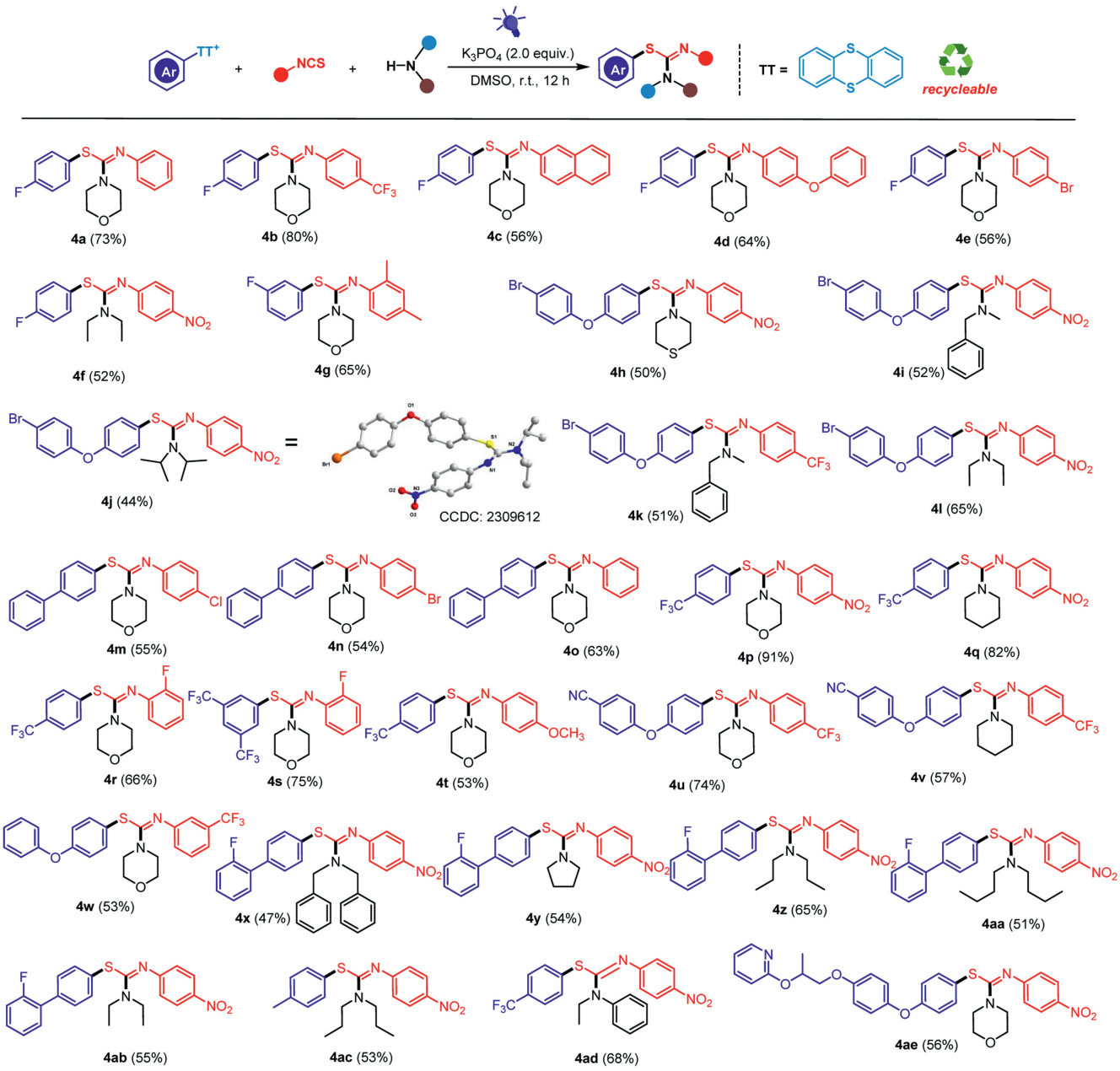


Entry	Variations from standard conditions	Yield (%) [b]
1	None	73
2	No base	47
3	No light	N.R.
4	Air instead of N_2	57
5	Other wavelengths instead of 455 nm	50–65
6	Solvents other than DMSO	Trace-58
7	DMSO/H_2O ($v_1/v_2 = 1:1$) instead of DMSO	36
8	Bases other than K_3PO_4	Trace-69
9	Heating instead of light	N.R.

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.3 mmol), **3a** (0.2 mmol), K_3PO_4 (0.4 mmol), at room temperature under irradiation with a 20 W blue LED (455 nm) for 12 h.
[b] Isolated yield. N.R. = no reaction.

Our initial optimization for the anticipated multicomponent reaction of aryl thianthrenium salt **1a**, isothiocyanatobenzene **2a**, and morpholine **3a** was summarized in Table 1. After a series of experiments, the desired product **4a** was obtained in 73% isolated yield when using 2.0 equiv. of K_3PO_4 as the base and DMSO as the solvent under the irradiation of a blue LED (20 W, 455 nm) for 12 h (Table 1, entry 1, see Supporting information for more details). In the absence of a base, the yield of the reaction is significantly decreased (Table 1, entry 2). In addition, the reaction could not occur without light irradiation (Table 1, entry 3). Under air conditions, the efficiency of the reaction will be greatly reduced (Table 1, entry 4). It is noteworthy that when 455 nm was replaced by other wavelengths, the yield of the desired product decreased (Table 1, entry 5). Further investigation of the solvent revealed DMSO gave the best result, and the use of mixed solvents could not improve the yield of the reaction (Table 1, entries 6 and 7). Replacing K_3PO_4 with other bases did not promote the yield of the product (Table 1, entry 8). Finally, controlled experiments show that heating alone does not promote the reaction (Table 1, entry 9).

After obtaining the optimized conditions, efforts were paid to the substrate scope of this transformation. As demonstrated in Scheme 2, various aryl thianthrenium salts **1** bearing electron-withdrawing groups (F, Br, CF_3, and CN) or electron-donating groups (Me and PhO) proceeded effectively with isothiocyanatobenzenes **2** and secondary amines **3** under the standard conditions giving the corresponding products in moderate to good yields (**4a**-**4ae**). However, the alkenyl or alkynyl thianthrenium salts were not compatible under the standard conditions (see Supporting information for more details). The exact structure of the product can be determined by single crystal X-ray diffraction (**4j**). Electron-effect and steric hindrance-effect have significant influence on the reaction efficiency. In general, aryl thianthrenium salts and aryl isothiocyanates bearing strong electron-deficient groups showed excellent reactivity in this transformation. Various cyclic or chain secondary aliphatic amines could participate in this reaction efficiently, show no obvious difference of reaction activity. Unfortunately, using alkyl isothiocyanate under the standard conditions delivered no desired products (see Supporting information for details). In addition, other types of amines were also investigated, only secondary amines could participate in the reaction (**4ad**) (see Supporting information for more details). More importantly, the visible-light-induced EDA

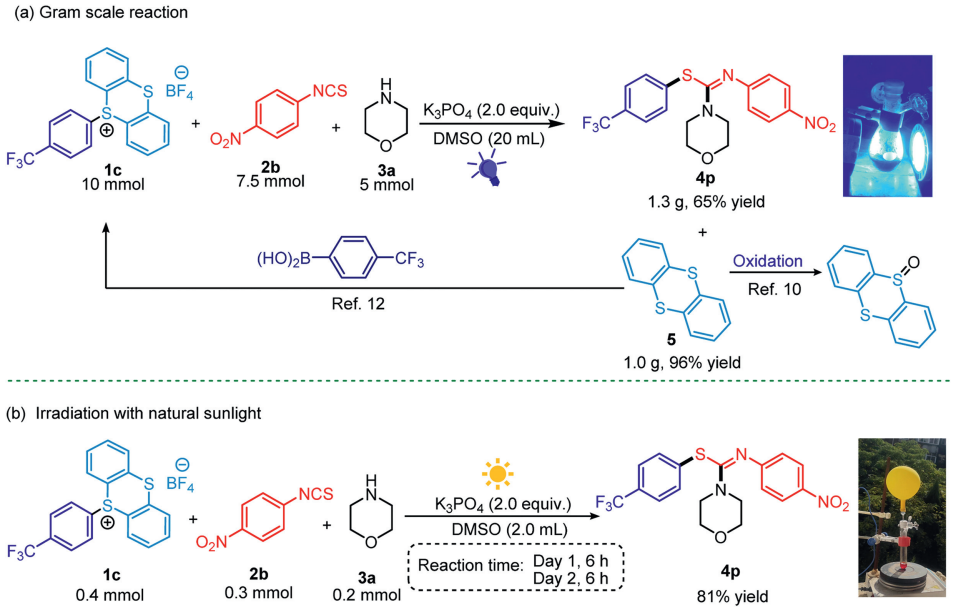


Scheme 2. The substrate scope. Reaction conditions: **1** (0.4 mmol), **2** (0.3 mmol), **3** (0.2 mmol), K_3PO_4 (0.4 mmol) at room temperature under irradiation with a 20 W blue LED (455 nm) for 12 h. Isolated yield.

complexation strategy was also applied to the late-stage functionalization of pharmaceuticals (**4ae**), suggesting the potential application value of this method.

To investigate the synthetic applications of this strategy, we implemented a gram-scale conversion by using the aryl thianthrenium salt **1c** (10 mmol), isothiocyanato-4-nitrobenzene **2b** (7.5 mmol), and morpholine **3a** (5 mmol) under irradiation of two 20 W blue LED lamps (Scheme 3a). To our satisfaction, the reaction proceeded well and resulted in the formation of product **4p** with a yield of 65%. Notably, thianthrene **5** was well recovered in quantitative yield which could react with arylboronic acids to produce thianthrenium salts. On the other hand, thianthrene **5** could also be oxidized into thianthrene 5-oxide which was used for further C–H thianthrenation of arenes (Scheme 3a). Furthermore, a sunlight-promoted experiment showed that the developed method could be carried out under sunlight conditions (Scheme 3b).

In order to obtain more detailed information about the reaction mechanism, some control experiments were carried out. When 3.0 equiv. of radical inhibitor (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) was added in the reaction system, the transformation was significantly suppressed, and a radical trapping intermediate **7** was detected by HRMS, suggesting aryl radical might be active radical species in the present transformation (Scheme 4). As seen in Fig. 1a, the **1b**, **2a**+**3a** did not show significant absorption in the visible light range, but a mixture of **1b**+**2a**+**3a** displayed an obvious red shift, showing the formation of an electron donor-receptor complex between **6** and **1b**. Subsequently, a Job's plot using UV–vis absorption experiments was drawn to evaluate the stoichiometry of the EDA complex between **1b** and **6**, where **6** was formed through the reaction of **2a** and **3a**. A Job's plot analysis confirmed the formation of a 1:1 complex between the **1b** and **6** (Fig. 1b). Furthermore, an on/off light-



Scheme 3. Synthetic applications.

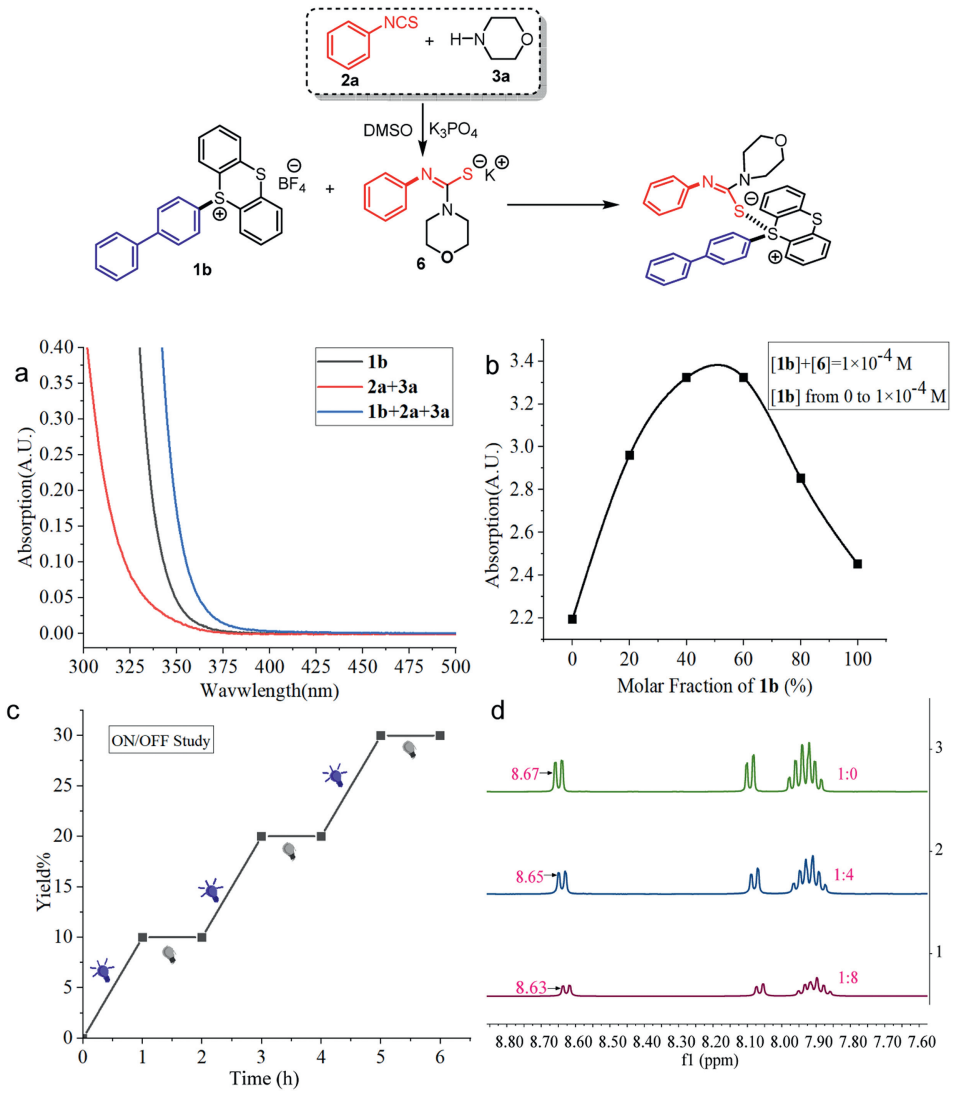
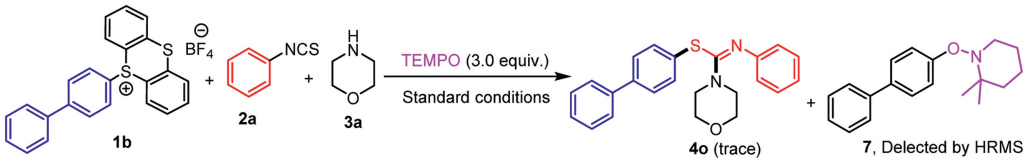
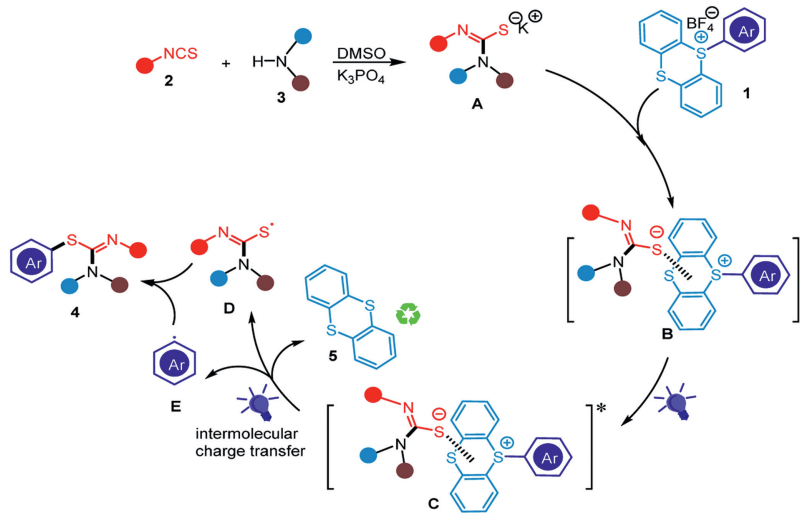


Fig. 1. (a) UV–vis absorption spectra of **1b**, **2a**+**3a**, and a mixture of **1b**+**2a**+**3a** (10^{-4} mol/L in DMSO). (b) Job's plot of **1b** and **6** in DMSO. (c) Visible light irradiation on/off experiment. (d) Titration experiments (^{1}H NMR shift of **1b** with **6**).



Scheme 4. Radical trapping experiment.



Scheme 5. Plausible mechanism.

irradiation experiment proved that the present transformation requires continuous illumination (Fig. 1c). Finally, upon addition of **6** formed *in situ* to **1b** in DMSO–d_6, the proton signals of **1b** showed obvious high-field shift. Thus, we confirmed that EDA complexes were formed between **1b** and **6** in the photochemical process (Fig. 1d).

On the basis of the above preliminary mechanistic studies, a plausible mechanism for this multicomponent reaction was proposed in Scheme 5. Firstly, in the presence of the K_3PO_4, secondary amines **3** reacted with isothiocyanatobenzenes **2** affording the corresponding thiolate **A**. Then, the electron-poor aryl thianthrenium salts **1** and electron-rich **A** thiolate anion associated to produce an EDA complex **B** which absorbed the energy of visible light to reach the excited state **C**. Subsequently, this excited EDA complex underwent a SET (single electron transfer) from the thiolate anion to the arylthianthrenium salt to give thiyl radical **D**, and aryl radical **E**. Finally, thiyl radical coupled with aryl radical, delivering the desirable product **4.**

In conclusion, we have demonstrated an efficient visible-light-induced EDA complex process for the synthesis of *S*-arylisothioureas under mild conditions. Compared with the previously reported methods, this light-driven one-pot multicompound domino reaction does not require any transition-metals or photocatalysts. Mechanism investigations support the strategy involving a photoinduced EDA complex and photocatalytic intermolecular charge transfer pathway. We also envisage that our results will provide more inspiration and ideas for the application of EDA mediated multi-component reactions in photocatalysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Guoju Guo: Writing – original draft, Data curation, Conceptualization. **Xufeng Li:** Methodology, Data curation. **Jie Ma:** Methodology. **Yongjia Shi:** Writing – original draft, Supervision. **Jian Lv:** Project administration, Investigation. **Daoshan Yang:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110024.

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