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可见光促进 C(3)(杂)芳硫基吲哚化合物的合成研究进展

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摘要 吲哚硫醚结构广泛存在于许多药物分子和天然产物分子中, 其衍生物具有抗菌、抗病毒及抗肿瘤等广泛的生物活性, 同时也是有机合成的重要中间体及药物合成的结构单元, 因此吲哚硫醚化合物在医药领域具有极大的应用价值. 其合成方法的研究也成为当前有机合成研究领域的热点之一. 特别是近年来, 可见光促进的吲哚 C(3)(杂)芳硫基化反应得到了快速的发展, 已成为制备吲哚硫醚类化合物的温和、高效合成方法之一. 综述了近年来可见光促进的吲哚硫醚类化合物的合成方法研究进展, 并对其部分反应机理做了相应的阐述.

关键词 吲哚硫醚; 光催化; C—S 键形成; 合成

Recent Progress of Visible Light-Induced the Synthesis of C(3) (Hetero)arylthio Indole Compounds

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Abstract The structure of 3-sulfenyl indoles widely exists in many drug molecules and natural product molecules. Its derivatives have extensive biological activities such as antibacterial, antiviral and anti-tumor, and are also important intermediates of organic synthesis and structural units of drug synthesis. Therefore, 3-sulfenyl indole compounds have great application value in the field of medicine. The research of its synthesis method has also become one of the current research hotspots. In this paper, the research progress in the synthesis of 3-sulfenyl indoles compounds in recent years is reviewed, and some reaction mechanisms are also discussed.

Keywords 3-sulfenyl indole; photocatalysis; C—S bond formation; synthesis

Indole is an important heterocyclic framework that exists in various natural products, drugs, and biologically active molecules.[1] Especially, 3-(hetero)aryl thioindole derivatives have biological activities such as antiviral [human immunodeficiency virus (HIV-1)],[2] anti allergic,[3] anti cancer,[4] anti-inflammatory,[5] and anti obesity.[6] For example, compound **A** can be used as an autotoxin inhibitor for treating fibrosis and cell proliferation diseases,[7] compound **B** can be used as a drug for treating respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD),[7] and compound **C** can be used as a local vasoconstrictor,[8] compound **D** has excellent anti proliferation effect on human breast cancer cell line MCF-7 by inhibiting tubulin polymerization,[9] and compound **E** has anti-inflammatory effect by inhibiting cyclooxygenase-2 (COX-2)[10] (Figure 1). Based on the important applications and medicinal value of indole derivatives containing (hetero)arylthio groups, the development of their synthesis methods has attracted great attention from chemical workers in recent years, and many efficient synthesis methods have been developed. The direct sulfenylation of C(3)—H bond of indole is the most direct and effective method to obtain 3-arylthioindoles. Despite great advantages have been made, there are still some limitations, including harsh reaction conditions, strong oxidants, not easily available precursors, and toxic metal salt catalysts.[11] Thus, there is still plenty of room to develop more environmentally benign, simple, and sustainable strategies for the 3-(hetero)aryl thioindole derivatives.

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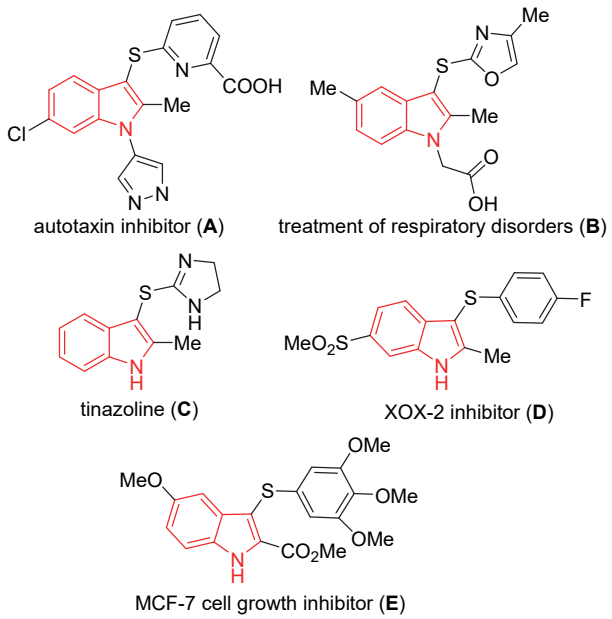


Figure 1 3-(Hetero)arylthio indole compounds with biological activity

In recent years, visible light promoted photoredox catalysis has attracted high attention from synthetic chemists and has been widely applied in organic synthesis.[12] And it provides new methods and pathways for many reactions that are difficult to complete under traditional thermochemical conditions.[13] The synthesis of 3-(hetero)aryl thioindole compounds induced by visible light has also been reported in related literature, and many photocatalysts have been applied in this conversion, such as transition metal Ru photosensitizers, non-metallic photosensitizers such as organic dyes (Eosin Y, Rose bengal, *etc.*), and organic photosensitizers (cecosporin, *etc.*), which are increasingly favored by researchers due to their low cost and toxicity. Furthermore, photocatalyst-free reaction systems have also been developed and applied in such reactions. Photocatalyst-free system not only reduces production costs and environmental pollution, but also greatly reduces the difficulty of product separation. There are two main mechanisms for the sulfenylation of indoles at the C(3)-position. One is the addition of sulfur radicals to indoles, and the other is the cross-coupling between sulfur radicals and indole radicals. This review categorizes the synthesis methods of 3-(hetero)arylthio indole derivatives based on the different substrates of the reaction. Specifically, there are two types: one is the coupling reaction between indole compounds and sulfides, and the other is the coupling reaction between 2-substituted phenylacetylene compounds and sulfides (Scheme 1). The generation of radicals in various reactions and the subsequent thiolation pathways were discussed, and their novelty and application value were evaluated. It is hoped that this review can provide new ideas for the application of aryl thiolation of indoles at the C(3)-position in organic synthesis and the synthesis of numerous high value-added indole molecules containing 3-aryl thiol groups.

1 Visible light-induced indole C(3) (hetero)aryl thiolation reaction

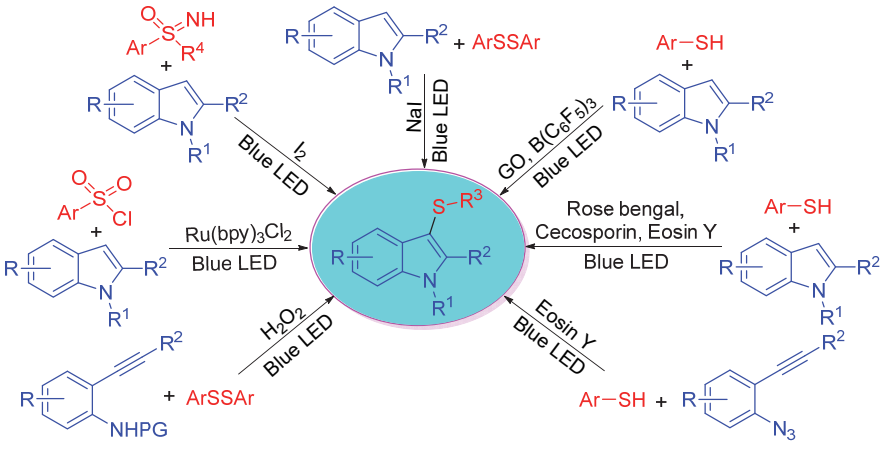
In recent years, the photochemical organic conversion promoted by visible light has attracted the interest of a large number of organic chemists. Compared with traditional methods, the photocatalytic oxidation using visible light as a renewable energy source has been demonstrated as a mild and powerful tool that can promote the activation of organic molecules through single electron transfer (SET) processes, thereby achieving many different types of organic conversion reactions.[14]

1.1 Coupling reaction between indole compounds and sulfides under visible light irradiation

1.1.1 Reactions involving sulfonyl chloride under visible light irradiation

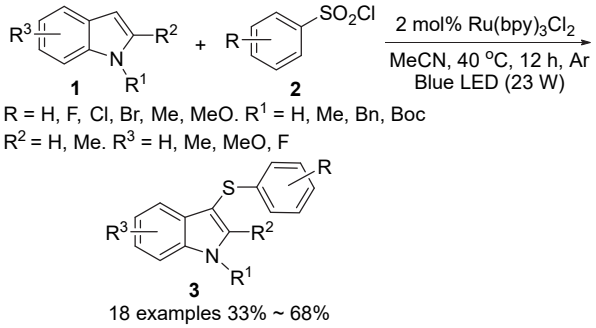
In recent years, metal photocatalysts have shown good catalytic performance in visible light promoted structural transformation of organic compounds and achieved excellent research results.[15] This synthesis method has become one of the mild and efficient synthesis methods for constructing C—C and C—S bonds.[16]

In 2012, Zheng and co-workers[17] developed a method for the synthesis of 1-methyl-3-(arylthio)-1*H*-indole under



Scheme 1 Synthesis route of 3-(hetero)arylthio indole compounds under visible light irradiation

mild conditions through the photoredox reaction of *N*-methylindole with arylsulfonyl chloride (Scheme 2). The cross-coupling reactions of various *N*-methylindoles with arylsulfonyl chlorides can be smoothly give corresponding coupling products **3** with moderate yields (33%～68%) in the presence of $Ru(bpy)_3Cl_2$ (2 mol%) in MeCN at 40 ℃ under blue LEDs irradiation for 12 h. The reaction system has good functional groups tolerance. The position of the substituent on the benzene ring of arylsulfonyl chlorides will affect the efficiency of the reaction. The steric hindrance of *o*-methyl leads to long reaction time and low yield of target compounds. The author proposed a possible mechanism as shown in Scheme 3. Firstly, the substrate indole **1** reacted with excited state $Ru(bpy)_3^{2+*}$ to generate intermediate **4** *via* reductively quenching pathway. Then, the key intermediate **7** was obtained through the three steps of the SET process. Finally, indole **4** attacked intermediate **7** to generate intermediate **8**, which was transformed into the product **3** with releasing a proton.

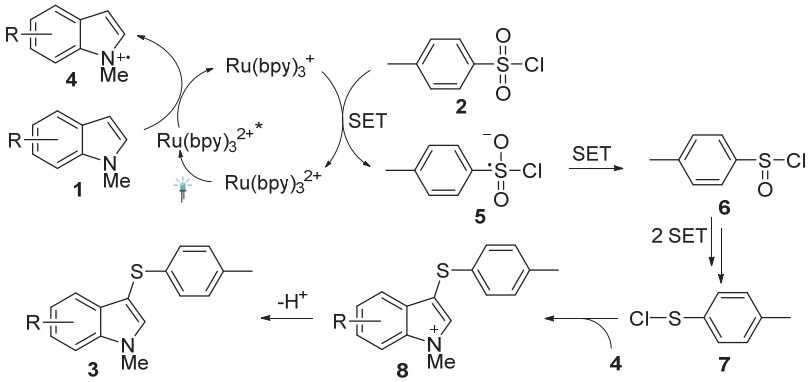


Scheme 2 Visible light induced photoredox-catalyzed reaction of indoles with arylsulfonyl chlorides

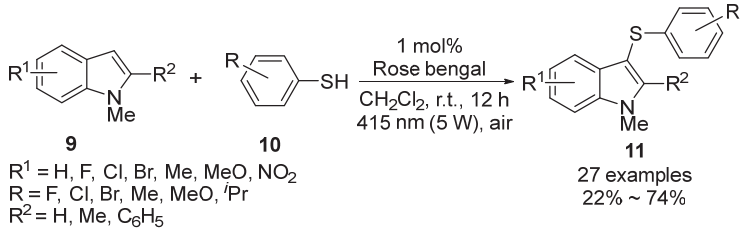
1.1.2 Reactions involving thiophenol under visible light irradiation

Although metal photocatalysts exhibit excellent catalytic performance in visible light induced structural transformation of organic compounds and have achieved excellent research results, they are not easily available. In recent years, many organic photocatalysts have also shown good catalytic activity in organic reaction induced by visible light, and have been widely applied in organic synthesis.[18]

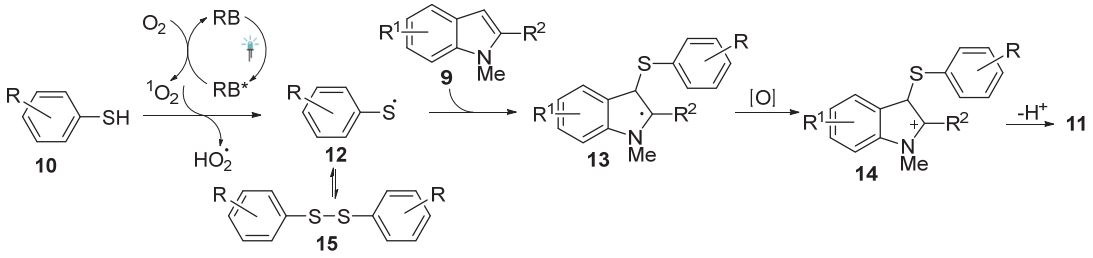
In 2017, Fan and co-workers[19] reported the method of preparing 3-arylthio indoles by blue light induced coupling reaction of indoles and thiophenols. They found that various indoles can be coupled with various thiophenols using 1 mol% Rose bengal (RB) as photocatalysts at room temperature in dichloromethane under blue LED irradiation for 12 h, and afforded the coupling products **11** in moderate to good yields (up to 74%) (Scheme 4). Indoles or thiophenols with electron-donating or electron-withdrawing substituents can be used in this system. This developed protocol has some merits including the use of broad substrate scope, good functional group tolerance, mild conditions, and not require any metal catalysts, bases, or peroxide oxidants, which demonstrates the high efficiency and practicality. The reaction employs readily available and inexpensive RB as photocatalyst and air as green oxidant. The author proposed a possible mechanism as shown in Scheme 5. Firstly, the RB was converted into the excited state species RB* under visible light irradiation, and this excited state species RB* interacted with O_2 to produce $^1O_2$ through energy transfer. At the same time, the excited state RB* changes to the ground state (RB). Then, the generated $^1O_2$ abstracts hydrogen atoms from thiophenol **10** to generate phenylthiyl radical **12**. The phenylthiyl rad-



Scheme 3 Possible reaction mechanism of the reaction of indoles with arylsulfonyl chlorides under visible light irradiation



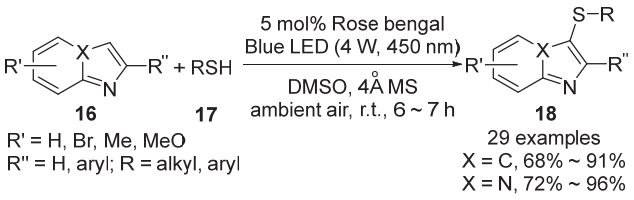
Scheme 4 Preparation of 3-arylthio indole compounds by photocatalyzed reaction of indoles with thiophenols



Scheme 5 Possible reaction mechanism of the coupling reaction of indoles with thiophenols under visible light irradiation

ical **12** reacted with indole **9** to afford a radical intermediate **13**. Finally, the intermediate **13** was oxidized to the carbocationic intermediate **14**, and then the product **11** was obtained by deprotonation of intermediate **14**. During this process, oxygen may then complete the photoredox cycle by oxidizing radical anions $RB^{\bullet-}$ to the ground state.

In 2018, Barman and co-workers[20] reported the regioselectivity aryl thiolation of thiophenols and indoles catalyzed by RB under blue light. They found that a variety of thiophenols can be coupled with indole derivatives (**16**) using 5 mol% RB as a photocatalyst in dimethyl sulfoxide (DMSO) at room temperature under blue light irradiation for 6～7 h, and 3-arylthioindoles were obtained in 68%～91% yields with a wide range of substrates scope (Scheme 6). At the same time, this method can also be applied in the aryl thiolation of imidazole pyridine derivatives, and the 3-arylthioimidazole pyridine derivatives were obtained in 72%～96% yields. The method has the advantages of simple operation, green and environment protection, high atom economy, and not require any metal catalysts and oxidants. It can be widely applied in organic synthesis and medicinal chemistry. For the reaction of thiophenols with indoles containing electron-donating or electron-with- drawing groups, corresponding 3-arylthioindoles products were also obtained with good yields.

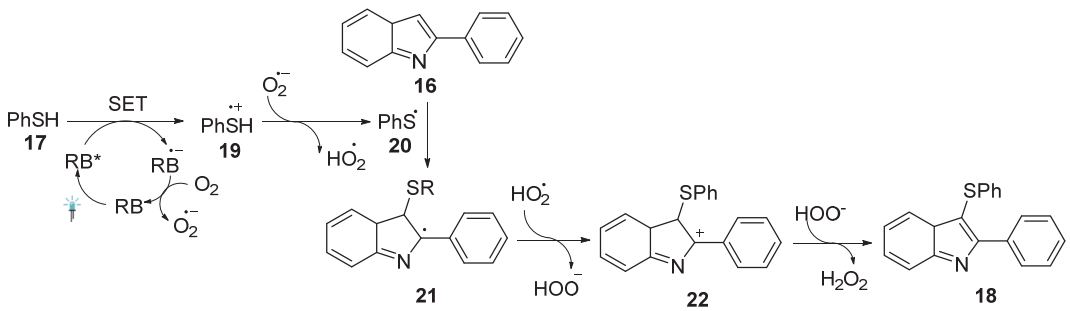


Scheme 6 Preparation of 3-arylthioindole compounds by blue light induced reaction of indoles with thiophenols

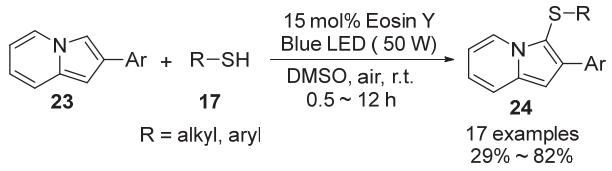
Based on previous literature reports[21] and control experiments, the author proposed a reaction mechanism as shown in Scheme 7. Firstly, RB was converted to the excited state RB* under the blue light irradiation. Then, a single electron transfer (SET) from thiol **17** to RB* afforded the radical cation **19** and $RB^{\bullet-}$. Subsequently, $RB^{\bullet-}$ was oxidized by air to afford the ground state RB and the radical anion of $O_2^{\bullet-}$. The deprotonation of the radical cation **19** by $O_2^{\bullet-}$ provided a stabilized phenylthiyl radical **20**. The generated phenylthiyl radical **20** reacted with compound **16** to form a radical intermediate **21**. Finally, **21** was oxidized by $HO_2^{\bullet}$ to generate carbocation **22** and HOO^-. The deprotonation of the carbocation **22** by HOO^- afforded the target product **18**. In this reaction, oxygen may play a crucial role in completing the photooxidation cycle by oxidizing the radical anion $RB^{\bullet-}$ to the ground state RB.

In 2020, Silveira and Lenardão[22] reported the synthesis of 3-sulfanyl indolizines from thiols and 2-arylindolizines induced by Eosin Y (EY) under blue light irradiation, using atmospheric oxygen as oxidant. They found that a variety of thiophenols can be coupled with 2-arylindolizines derivatives (**23**) using 15 mol% EY as photocatalyst in DMSO at room temperature under blue light irradiation for 0.5～12 h, and the 3-sulfanyl indolizines were obtained in 29%～82% yields (Scheme 8). Importantly, the corresponding 1,3-bissulfanyl indolizines were obtained with good yields by the use of a catalytic amount of I_2 (Scheme 9). The reaction mechanism is similar to Scheme 7.

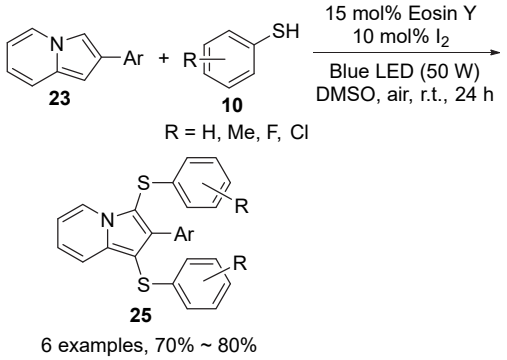
In another systematic research work, Barman and co-workers[23] reported an efficient method for the synthesis of 3-arylthioindoles from indoles and thiophenols under blue light irradiation (Scheme 10). They found that varies thiophenols can coupled smoothly with indoles using 1 mol% cecosporin (CS) as a photocatalyst in 1,4-dioxane at



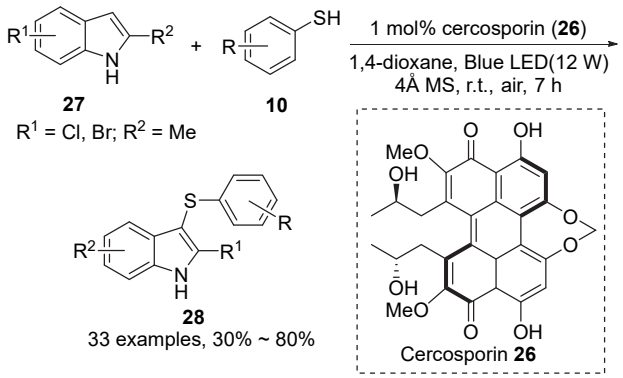
Scheme 7 A plausible mechanism of the reaction of indoles with thiophenols under blue light irradiation



Scheme 8 Visible-light induced sulfenylation of indolizines with thiophenols

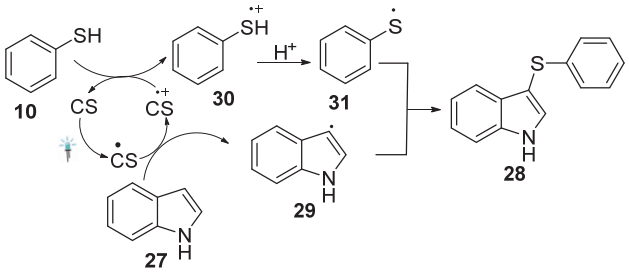


Scheme 9 Visible-light induced synthesis of 1,3-bissulfanyl indolizines



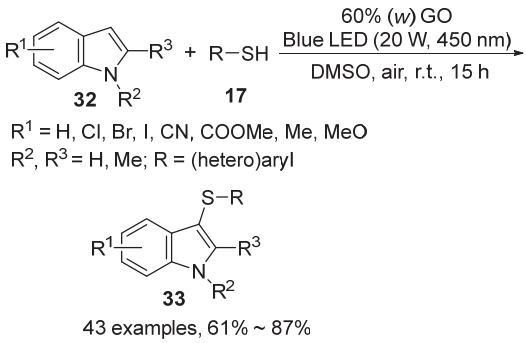
Scheme 10 Visible-light induced sulfenylation of indoles with thiophenols

room temperature under blue light irradiation for 7 h, and the 3-arylthioindoles were obtained in 30%～80% yields. The developed method features a wide range of functional group tolerances. Thiophenols bearing electron-donating or electron-withdrawing groups reacted with indoles to afford the corresponding products in good yields. The author proposed a reaction mechanism as shown in Scheme 11. Mechanism investigation indicated that the transformation involves a radical pathway. Firstly, CS was converted into excited state species CS* by blue light irradiation. Subsequently, CS* reduced indole **27** to generate a radical intermediate **29** and CS radical cation $CS^{\bullet+}$. $CS^{\bullet+}$ oxidized thiophenol to generate thiol radical cation **30** and CS. Finally, the thiol radical cation **30** underwent deprotonation to generate the stabilized phenylthiyl radical **31**, and then the phenylthiyl radical **31** reacted with the radical intermediate **29** to provide the corresponding product **28**.



Scheme 11 Possible reaction mechanism of the visible light induced sulfenylation of indoles with thiophenols

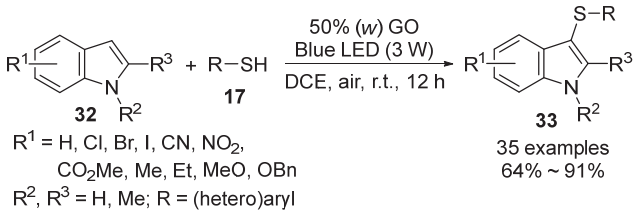
In the same year, Liu and co-workers[24] reported a new effective method to prepare the 3-aryl thioindoles under blue light irradiation using graphite oxide (GO) as accelerator. The author found that varies indoles can coupled smoothly with thiophenols using 60% (*w*) GO as a promoter under blue light irradiation for 15 h in DMSO at room temperature, the corresponding products 3-aryl thioindoles were obtained in 61%～87% yields (Scheme 12). This reaction system is effectively compatible with indoles or thiophenols containing different electron-donating or electron-withdrawing groups. This reaction system can be applied for gram scale synthesis, and it can also be applied for the preparation of 3-aryl selenides and 3-thiocyano indoles. The method has the advantages of simple operation, high yield of 3-aryl thioindoles, and not require metal catalysts and iodine. Moreover, the non-toxic and easily treatable GO was used as the oxidant in this reaction system. At the same time, GO can be recycled.



Scheme 12 Visible light induced sulfenylation of indoles C(3) in the presence of 60% (*w*) GO promoter

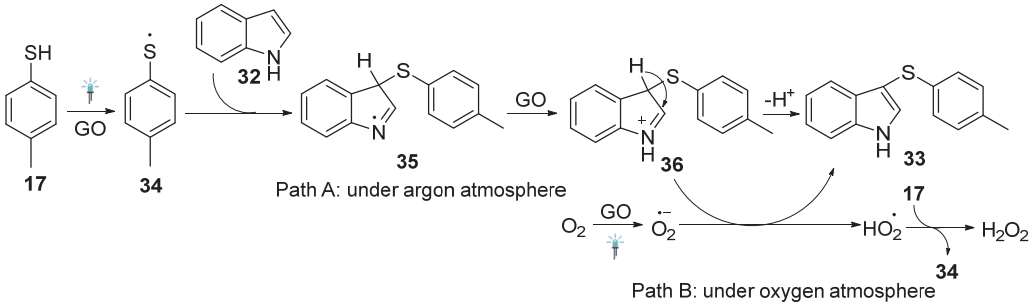
Later, the same research group[25] further improved the reaction system by using 50% (*w*) GO as oxidant and photocatalyst, 1,2-dichloroethane (DCE) as solvent, and blue light irradiation. 3-Aryl thioindole products were obtained with 64%～91% yields under blue light irradiation for 12 h in DCE at room temperature (Scheme 13). This system was suitable for both aryl thiophenols and heteroaryl thiols. At the same time, the system can also undergo indoles C(3) thiocyanation reaction, and the corresponding products were obtained with 43%～85% yields. All reactions proceeded smoothly when thiophenols have electron-donating or electron-withdrawing groups on the phenyl ring. At the

same time, the electron negativity of the substituents plays a major role in the reactivity of the substrates. In this transformation, substrates with electron-donating substituents show better reaction results than substrates with electron-withdrawing substituents. Mechanism studies showed that GO probably plays a crucial role during the process of oxidation and deprotonation. Based on the experimental results and relevant literature,[24,26-27] the author proposed a possible mechanism for the reaction, as shown in Scheme 14. In path A, under the blue LED irradiation, 4-methylbenzenethiol transformed into phenylthiyl radical **34** promoted by the functional groups on the surface of GO. Then, the phenylthiyl radical **34** reacted with **32** to produce the radical intermediate **35**. Subsequently, **35** was oxidized to generate the intermediate **36**. Finally, deprotonation of intermediate **36** provided the product **33**. In path B, under the blue LED irradiation, the unpaired electrons in GO activated oxygen through the SET process to produce the oxygen radical anion ($O_2^{\bullet-}$),[28] and the oxygen radical anion ($O_2^{\bullet-}$) abstracted the proton from **36** to produce the desired product **33** and perhydroxyl radical ($HO_2\bullet$). Perhydroxyl radical ($HO_2\bullet$) abstracted the proton from compound **17** to form hydrogen peroxide and the phenylthiyl radical **34**.



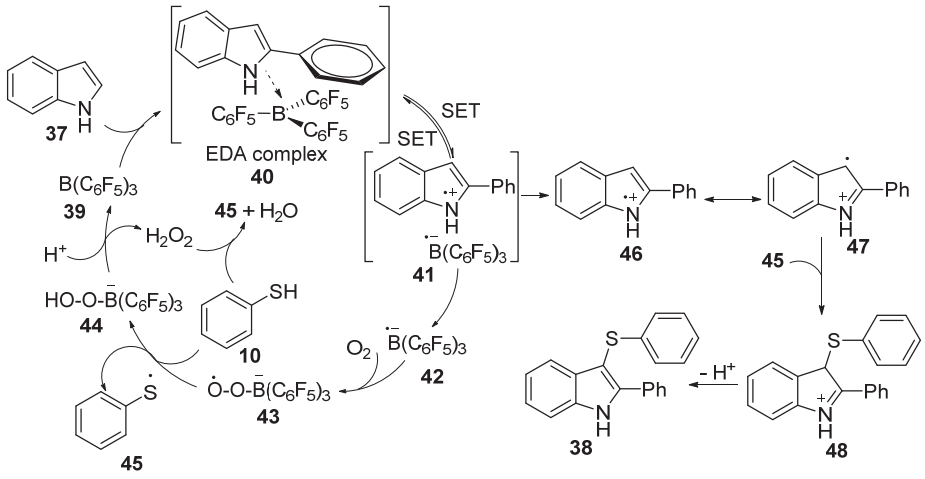
Scheme 13 Visible light induced sulfenylation of indoles C(3) in the presence of 50% (*w*) GO promoter

The pioneering work of Melchiorre[29a] and Xu[29b] shows that photoexcited electron donor-receptor (EDA) complexes have significant reactivity under mild metal-free and peroxide-free conditions. This method has been widely applied in the formation of C—C bonds, and has achieved excellent research results.[30] In 2021, Tang and co-workers[31] reported the aryl thiolation reaction of indoles with thiophenols catalyzed by $B(C_6F_5)_3$ under visible light irradiation. They found that a variety of indoles **37** can be coupled with thiophenols **10** using 5 mol% $B(C_6F_5)_3$ in DCE under blue light irradiation in air. Under the optimum conditions, all cross-coupling reactions were completed at room temperature in 7～14 h and the corresponding products 3-aryl thioindoles were obtained with 50%～99% yields (Scheme 15). Naphthalene-2-thiol can also undergo a smooth reaction in this system, and the target product was obtained with 80% yield. Both electron rich and electron deficient thiophenols were suitable for this reaction system. This reaction system has the advantages of good substrate tolerance, strong functional group compatibility, and not require transition metals. Mechanism studies showed that the single electron transfer (SET) process plays an important role in the EDA complex formed by $B(C_6F_5)_3$ and indoles in the catalytic cycle of $B(C_6F_5)_3$. The possible reaction mechanism is shown in Scheme 16. The EDA complex **40** was formed by $B(C_6F_5)_3$ and indole underwent a SET process under blue light irradiation to generate the radical ion pairs **41**, **41** underwent back electron transfer (BET)[28b] to regenerate the ground state EDA complex **40**. Radical anion **42** reacted with oxygen to form intermediate **43**, which abstracted a hydrogen atom from **10** and generated intermediate **44** and thiol radical **45**. The intermediate **44** was protonated to provide $B(C_6F_5)_3$, and hydrogen peroxide was released to complete the catalytic



Scheme 14 The proposed mechanism for the sulfenylation of indoles C(3) in the presence of 50% (*w*) GO promoter

Scheme 15 $B(C_6F_5)_3$-catalyzed aerobic oxidative C—S cross-coupling reaction of thiophenols with indoles under visible light irradiation

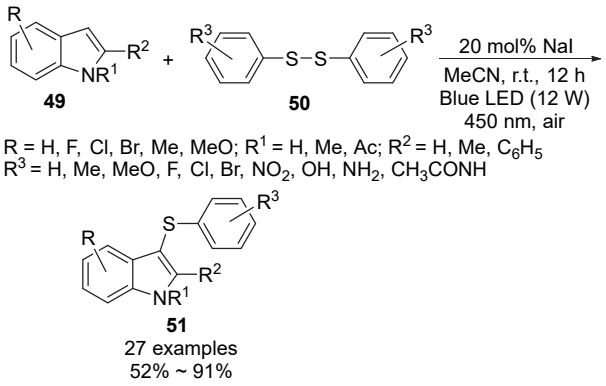


Scheme 16 Possible reaction mechanism of the coupling reaction of thiophenols with indoles under visible light irradiation

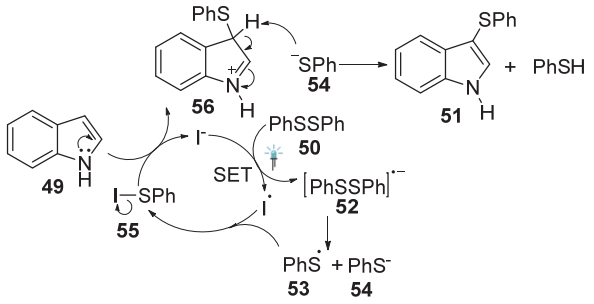
cycle. The released hydrogen peroxide oxidized **10** and generated phenylthiyl radical **45** and water. Intermediate **45** reacted with **47** to form intermediate **48**, and intermediate **48** was directly deprotonated to give final product **38**.

1.1.3 Reactions involving disulfides under visible light irradiation

In 2017, Yan and co-workers[32] reported an efficient method for the synthesis of 3-arylthioindoles from indoles and diaryldisulfides catalyzed by NaI under visible light conditions (Scheme 17). They systematically investigated the cross-coupling reactions of indoles with diaryldisulfides using 20 mol% NaI in acetonitrile at room temperature. The corresponding products of 3-arylthioindoles were obtained in moderate to good yields under visible light irradiation for 12 h (Scheme 17). This reaction system has the advantage of a wide range of substrates. The author proposes a possible mechanism as shown in Scheme 18. Firstly, diphenyl disulfide **50** was initially activated under visible light irradiation. A single electron transfer from iodide anion (I^-) to the activated diphenyl disulfide provided a diphenyl disulfide anion radical **52** and iodine radical ($I^•$). The cleavage of anion radical **52** provided the thiophenol anion **54** and phenylthiyl radical **53**. The aryl



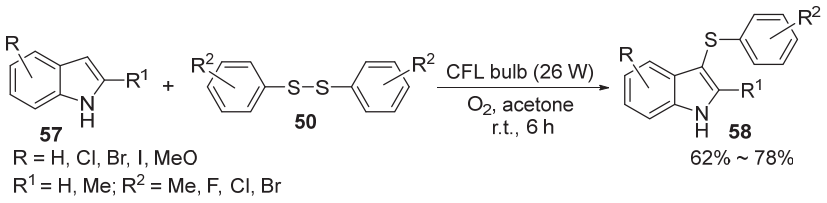
Scheme 17 Visible light-induced C(3) sulfenylation of indoles with diaryl disulfides



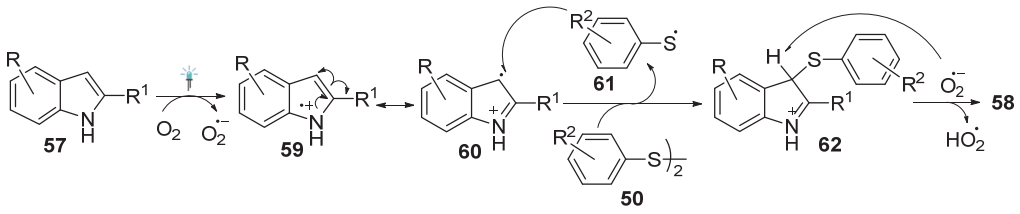
Scheme 18 Possible reaction mechanism of the C(3) sulfenylation of indoles with diaryl disulfides under visible light irradiation

sulfenyl iodine **55** was obtained by coupling the iodine radical ($I^•$) and phenylthiyl radical **53**. Finally, electrophilic substitution with the indole provided the 3-arylthioindole product **51**.

A similar strategy was developed by the group of Kumar. In 2019, they[26] developed a photocatalyst and transition metal-free visible light promoted method for the formation of C—S bond that provided 3-arylthioindoles using oxygen as benign oxidant. They found that a variety of diaryl disulfide derivatives **50** could be coupled with indole reagents **57** using oxygen as oxidant in acetone at room temperature. Under standard reaction conditions, all cross-coupling reactions can be completed in 6 h and the coupling products 3-aryl thioindoles were obtained in 62%～78% yields (Scheme 19). The developed method is amenable and sustainable for potentially operational procedures, and various diarylsulfides and indoles are well tolerated in the present transformation. The reaction system was also compatible with diaryl diselenide, but the reaction system was not suitable for dialkyl disulfides. The author proposed a reaction mechanism as shown in Scheme 20. Firstly, indole **57** was excited by visible light and reacted with oxygen to produce the superoxide radical anion $O_2^{•-}$ and indole radical cation **59**. Indole radical cation **59** formed a stabilized resonance equation **60**. Then **60** reacted with diaryl disulfide **50** to form 3-aryl thioindole



Scheme 19 Photocatalyst-free, visible light-induced C(3) sulfenylation of indoles



Scheme 20 Possible reaction mechanism of the C(3) sulfenylation of indoles under visible light irradiation

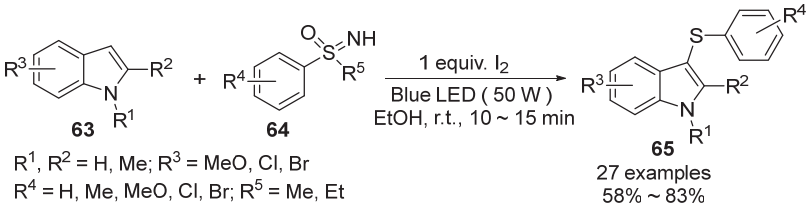
cation **62** and phenylthiyl radical **61** (PhS•). Finally, the superoxide radical anion $O_2^{\bullet-}$ abstracted a proton from cation **62** to afford the target product **58**.

1.1.4 Reactions involving sulfoximines under visible light irradiation

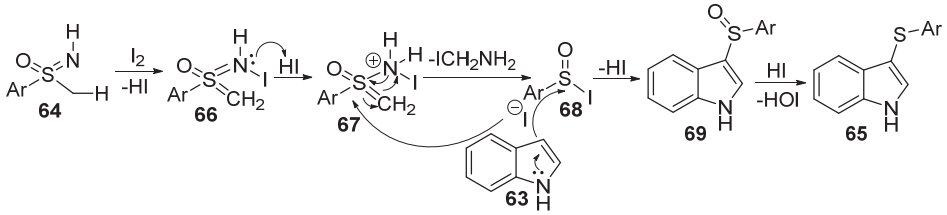
In 2023, Nandi and co-workers[33] reported a new effective method to prepare the 3-arylsulfenylindoles in the presence of I_2 under blue light irradiation. The author found that varies indoles can be coupled smoothly with sulfoximines in the presence of 1 equiv. of I_2 under blue light irradiation for 10～15 min in EtOH at room temperature, the corresponding products 3-arylsulfenylindoles were obtained in 58%～83% yields (Scheme 21). The reaction system was effectively compatible with indoles or sulfoximines containing different electron-donating or electron-withdrawing groups. This method has the advantages of fast reaction speed, mild reaction conditions, a wide range of substrates, and not require metals and photocatalysts. Based on the experimental results and relevant literature,[34] the author proposed a possible mechanism for the reaction, as shown in Scheme 22. Coordination of I_2 with sulfoximine **64** gave intermediate **66**, which reacted with HI (liberated in the first step) to generate **67**. Subsequent nucleophilic attack of iodide on **67**, followed by intramolecular rearrangement provided the sulfinyl iodide **68** with liberation of (iodomethyl)amine. Finally, **68** reacted with indole **63** to produce the 3-arylsulfinylindole **69**, which underwent rapid deoxidation in the presence of HI to deliver the 3-sulfenylindole **65**.

1.2 Coupling reaction between 2-substituted phenylacetylene compounds and sulfides under visible light irradiation

In recent years, photocatalytic redox reactions without photocatalysts have also achieved great development and excellent research results.[35] In 2017, Wang and co-workers[36] developed an efficient and convenient strategy to synthesize 3-arylthioindole by promoting the domino cyclization of 2-alkynylaniline with disulfides under blue light irradiation (Scheme 23). In the presence of 1 equiv. of H_2O_2, the tandem oxidative cyclization of 2-alkynylanili-

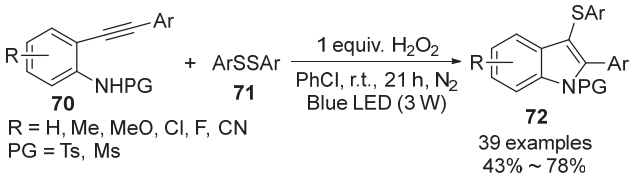


Scheme 21 Visible light induced sulfenylation of indoles C(3) in the presence of I_2.



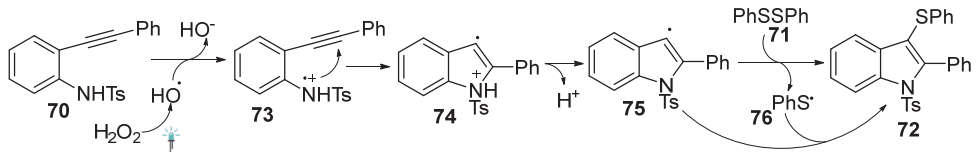
Scheme 22 Proposed mechanism for the sulfenylation of indoles C(3) in the presence of I_2 under blue light irradiation

nes with disulfides was induced by blue light irradiation to provide the corresponding 3-arylthioindole products in good yields. This method has the advantages of mild reaction conditions, a wide range of substrates, and not require metals and photocatalysts. Furthermore, it is also compatible with diaryl diselenium compounds, and it can also undergo aryl selenization reactions. However, this system was not suitable for dialkyl disulfides. The author proposed the reaction mechanism as shown in Scheme 24. Firstly, H_2O_2 was split under blue visible light to produce hydroxyl radical, and hydroxyl radical combined with 2-alkynylaniline **70** to afford the intermediate **73**. Then, intermediate **73** underwent intramolecular cyclization to form intermediate **74**, which deprotonated to form intermediate **75**. Finally, intermediate **75** reacted with diphenyl disulfide **71** to afford the final product 3-phenylthioindole derivative **72**, while generating phenylthiyl radical **76**. **76** reacted with **75** to form the product 3-phenylthioindole **72**.

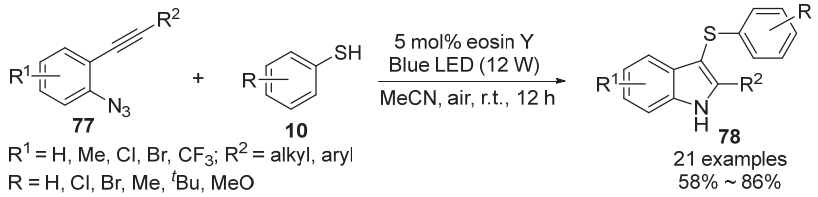


Scheme 23 Visible-light-induced tandem oxidative cyclization of 2-alkynylanilines with disulfides

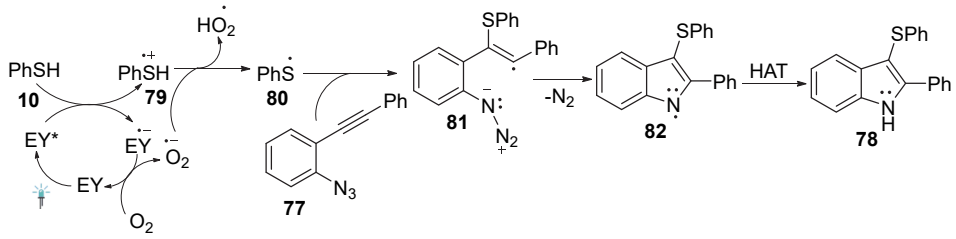
In 2018, Kshirsagar and co-workers[37] reported the strategy of using organic dyes as photocatalysts for the regionally specific radical cascade cyclization of 2-alkynyl azides and thiophenols to prepare the 3-arylthioindoles. Under blue light irradiation, all reactions can be completed at room temperature for 12 h using 5 mol% EY as a photocatalyst, and air as a benign oxidant in acetonitrile, and the 3-arylthioindoles were obtained in 58%～86% yields (Scheme 25). Moreover, alkyl thiols can also be applied to this reaction system and the corresponding 3-alkylthioindoles can be obtained smoothly. This reaction has the advantages of mild reaction conditions, wide substrates range, and not require any metal catalysts. Especially, the reaction process is green and environmental benign due to use air as a green oxidant. Based on experimental results and relevant literature,[21] the author proposed a radical cascade reaction pathway as shown in Scheme 26. Firstly, under blue light irradiation, the organic photocatalyst Eosin Y (EY) was transformed into excited state Eosin Y (EY*). The excited state EY* carried out single electron oxidation of thiophenol to provide radical cation species **79**, while EY* was reduced to radical anion $EY^{\bullet-}$, which can be reoxidized to the ground state through air oxygen to generate EY and $O_2^{\bullet-}$. Deprotonation of radical cation **79** provided phenylthiyl radical **80**. The regioselectivity addition of phenylthiyl radical **80** to the triple bond of compound **77** provided the radical intermediate **81**. The radical intermediate **81** underwent intramolecular cyclization and released N_2 to produce a *N*-center radical **82**. The transfer of hydrogen radicals from the hydrogen source present in the reaction mixture provided product **78**.



Scheme 24 Possible reaction mechanism of the tandem oxidative cyclization of 2-alkynylanilines with disulfides under visible light irradiation



Scheme 25 Visible light induced reaction of 2-alkynyl azide with thiophenols to prepare 3-arylthio indole compounds



Scheme 26 A plausible mechanism of the reaction of 2-alkynyl azides with thiophenols under visible light irradiation

2 Summary and Outlook

In the past few years, the construction of C—S bonds through direct C—H sulfenylation reactions has rapidly advanced and become an eco-friendly synthetic tool for pharmacists and organic chemists. Herein, an overview of the recent progress in C—S bond sulfenylation of indoles C(3) position under visible light irradiation is presented. This type of reaction has the advantages of green and environmental protection of visible light reaction and mild reaction conditions.[38] Although significant progress has been made in the synthesis of such compounds through photocatalysis, the efficient and highly selective synthesis of indole-3-thioethers with diverse structures is still a major challenge in this field. So, there are still some areas that need to be improved. Firstly, some reaction systems need to use of expensive and difficult to recover photoreduction catalysts, such as Ru. Secondly, most of sulfenylation of indoles occurred at C(3) position, while there is limited research on C(2)—H sulfenylation and C(2)/C(3)—H disulfenylation. Thirdly, the visible-light-induced C—S bond construction reaction directly using sulfur powder as the sulfur source has not been achieved thus far. Moreover, the synthesis of sulfenylindoles having reactive hydrogen functional groups (peculiarly NH_2 and CO_2H) need further to be probed. In short, there are still many challenges and opportunities in the research field of photocatalytic C—S bond formation. For example, in the future research, more attention should be paid to the study of photocatalyst-free reaction systems and the exploration of catalytic asymmetric conversion of such reactions. We believe that some more efficient, selective and novel reaction systems will emerge in the future, and these reactions will play an important role in organinc synthesis.

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