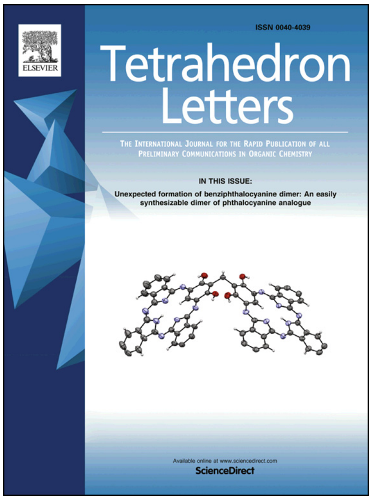


Visible-light promoted synthesis of 3-arylthioindoles from indoles and diaryl disulfides

Lin-miao Ye, Jie Chen, Peng Mao, Xue-jing Zhang, Ming Yan

PII: S0040-4039(17)30698-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.05.090
Reference: TETL 48983

To appear in: *Tetrahedron Letters*

Received Date: 19 April 2017
Revised Date: 28 May 2017
Accepted Date: 31 May 2017

Please cite this article as: Ye, L-m., Chen, J., Mao, P., Zhang, X-j., Yan, M., Visible-light promoted synthesis of 3-arylthioindoles from indoles and diaryl disulfides, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.05.090

Tetrahedron Letters
journal homepage: www.elsevier.com

Visible-light promoted synthesis of 3-arylthioindoles from indoles and diaryl disulfides

Lin-miao Ye, Jie Chen, Peng Mao, Xue-jing Zhang, and Ming Yan*

Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
photoirradiation
synthesis
3-arylthioindole
disulfide

ABSTRACT

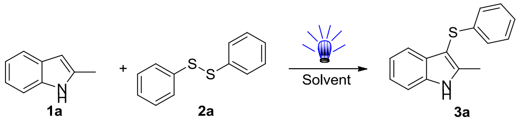
3-Arylthioindoles could be synthesized in good yields via the photoirradiation of indoles and disulfides. The reaction is efficiently promoted by the catalytic amount of sodium iodide. A reaction mechanism involving the electrophilic substitution of indoles with arylsulfenyl iodine intermediates is suggested.

Indoles are important heterocyclic compounds which are widely found in natural products and pharmaceuticals[1]. Among them, 3-thioindoles are of great interest due to their diverse biological and pharmacological properties, such as antitumor[2], anti-HIV[3], antiallergic[4] and anticardiovascular[5] activities. Thus, the synthesis of 3-thioindoles has attracted great attentions over the past decades. Thiols[6], sulfonyl halides[7], sulfonyl hydrazides[8], *N*-thioimides[9] and sulfonium salts[10] were used as the source of organic sulfur moiety to synthesize 3-sulfenyl indoles. Disulfides were also applied for the 3-sulfenylation of indoles in the presence of metal catalysts[11], iodine[12], oxidants[13] and bases[14]. Microwave irradiation was reported to promote the reaction[15]. Recently, Lei reported an electrocatalytic protocol for the synthesis of 3-arylthioindoles from indoles and disulfides[16].

In recent years, visible-light-mediated reactions have emerged as one attractive strategy for organic synthesis[17]. The methods are safer, cleaner and more environmentally friendly. Recently, we developed the synthesis of benzothiophenes and benzothiazoles via visible-light promoted reactions of diaryl disulfides[18]. The generation of arylthiyl radical through the homolysis of diaryldisulfides is proposed as the crucial initiation step. Herein, we report an efficient synthesis of 3-arylthioindoles from diaryl disulfides and indoles under the irradiation of visible light.

Initially, the reaction of 2-methylindole **1a** and diphenyl disulfide **2a** was examined with the irradiation of a 12 W blue LED under an air atmosphere. No expected product **3a** was obtained after 18 h. To our delight, the product **3a** was obtained in a good yield when a catalytic amount of sodium iodide was added. The reaction conditions were further examined and the results are summarized in Table 1. Among the tested iodide sources, sodium iodide afforded the best yield (Table 1, entries 2-6). The reaction could be conducted under argon or oxygen atmosphere, however lower yields were obtained (Table 1, entries 7-8 *vs.* entry 2).[19] A screening of reaction solvents demonstrated acetonitrile as the best choice (Table 1, entries 9-13). Other lights with different wavelengths (254 nm, 365 nm and 530 nm) could also promote the reaction, but low yields were observed (Table 1, entries 14-16). The reaction did not occur upon the exclusion of the photoirradiation (Table 1, entry 17). The increase or the decrease of the loading of **2a** led to lower yields (Table 1, entries 18-19).

Table 1. Screening of reaction conditions.



Entry	Solvent	Additive (mol%)	Light source	Yield (%)[a]
1	MeCN	-	450 nm	0
2	**MeCN**	**NaI (20)**	**450 nm**	**89(83[b])**
3	MeCN	KI (20)	450 nm	76
4	MeCN	TBAI (20)	450 nm	13
5	MeCN	NaI (10)	450 nm	85
6	MeCN	NaI (30)	450 nm	88
7[c]	MeCN	NaI (20)	450 nm	23
8[d]	MeCN	NaI (20)	450 nm	43
9	EtOAc	NaI (20)	450 nm	42
10	DCM	NaI (20)	450 nm	61

---

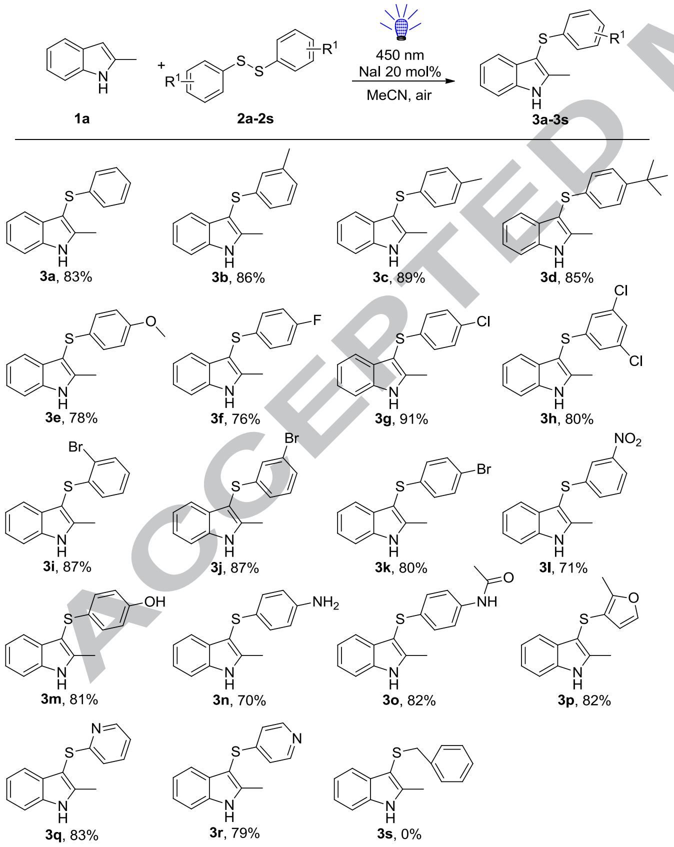
* Corresponding author. Tel.: +86-20-39943049; fax: ++86-20-39943049; e-mail: yanming@mail.sysu.edu.cn

11	EtOH	NaI (20)	450 nm	52
12	THF	NaI (20)	450 nm	15
13	Toluene	NaI (20)	450 nm	65
14	MeCN	NaI (20)	254 nm	42
15	MeCN	NaI (20)	365 nm	31
16	MeCN	NaI (20)	530 nm	8
17[e]	MeCN	NaI (20)	-	0
18[f]	MeCN	NaI (20)	450 nm	80
19[g]	MeCN	NaI (20)	450 nm	88

Reaction conditions: indole **1a** (0.3 mmol), disulfide **2a** (0.3 mmol), solvent (2 mL), photoirradiation with a 12 W blue LED, room temperature, 18 h. [a] GC yield with *n*-dodecane as the internal standard. [b] Isolated yields after the column chromatography. [c] Under an argon atmosphere. [d] Under an oxygen atmosphere. [e] Reaction performed in the dark. [f] **2a** (0.25 mmol) was used. [g] **2a** (0.35 mmol) was used.

With the optimized reaction conditions in hand, the scope of disulfides was examined and the results are summarized in Table 2. Diphenyl disulfides bearing with electro-donating groups such as methyl, *t*-butyl and methoxyl were tolerated well. The corresponding products (**3b-3e**) were obtained in good yields. The substitutions with fluoro, chloro, and bromo did not affect the yields (**3f-3k**). The substrate **2l** containing a nitro group gave the product **3l** in a moderate yield. Functional groups such as hydroxyl, amino and amide were also tolerated well. The corresponding products **3m-3o** were prepared in 70-82% yields. The reaction of heteroaryl disulfides (**2p-2r**) provided the products in good yields. However, dibenzyl disulfide **2s** was found to be unreactive. No expected product **3s** was obtained.

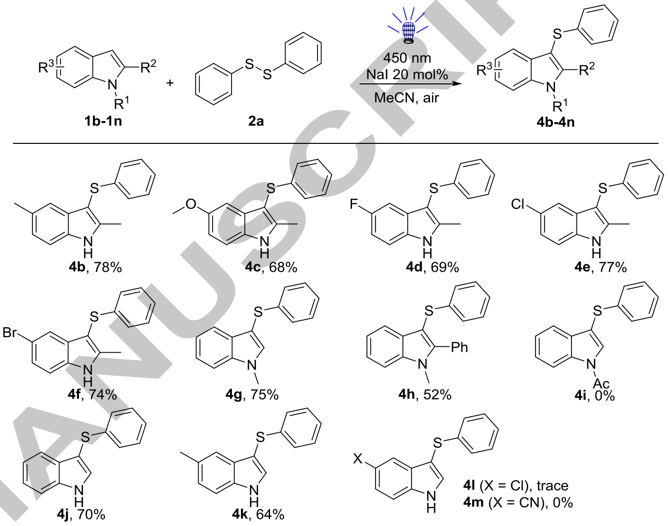
Table 2. Scope of disulfides.[a,b]



[a]Reaction conditions: **1a** (0.3 mmol), **2a-2s** (0.3 mmol), MeCN (2.0 mL), photoirradiation with a 12 W blue LED, room temperature, 18 h. [b] Isolated yields.

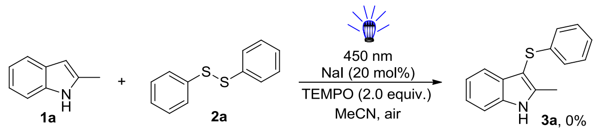
Furthermore, a series of substituted indoles were examined and the results are summarized in Table 3. Generally, the indoles substituted with methyl, methoxy, and halogen reacted smoothly to provide the corresponding products in moderate yields (**4b-4f**). *N*-methylindole **1g** gave the product **4g** in a moderate yield. The reaction of *N*-methyl-2-phenyl-indole **1h** delivered the product **4h** in a low yield. The steric hindrance of 2-phenyl group may affect the transformation. *N*-acetylindole **1i** is unreactive in the reaction. The reaction of unsubstituted indole **1j** gave the product **4j** in a moderate yield. 5-Methylindole **1k** provided the desired product **4k** in a moderate yield. Unfortunately, indoles containing electron-withdrawing groups such as chloro and cyano were unreactive (**4l-4m**). Only trace amount of the product **4l** was detected by GC-MS.

Table 3. Scope of indoles.[a,b]



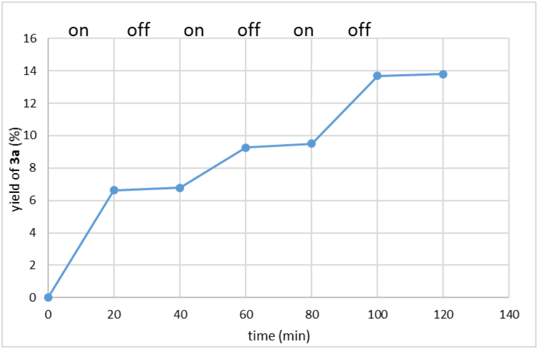
[a]Reaction conditions: **1b-1j** (0.3 mmol), **2a** (0.3 mmol), MeCN (2.0 mL), photoirradiation with a 12 W blue LED, room temperature, 18 h. [b] Isolated yields.

To gain the insight into the reaction mechanism, the radical scavenger TEMPO was added. The reaction was completely inhibited. The result supported a radical pathway (Scheme 1).



Scheme 1. Radical trapping experiment.

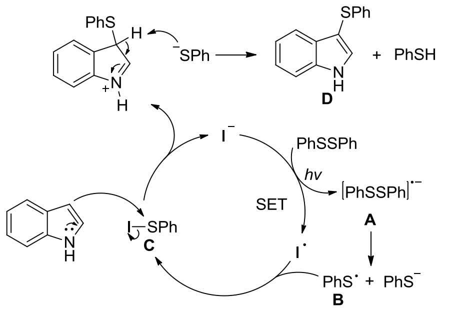
Furthermore, the effect of photoirradiation was examined through the ON/OFF light experiment (Scheme 2). The reaction proceeded smoothly under the irradiation of visible-light. The conversion stopped when the light source was removed. The result excluded a radical chain reaction mechanism.



Scheme 2. ON/OFF light experiment.

The UV-vis spectra of diphenyl disulfide, sodium iodide, 2-methylindole, and the reaction mixture were examined under the different concentrations (see support information for the details). None of them showed the strong absorptions around 450 nm. The maximum absorption peaks of diphenyl disulfide solutions were observed around 350 nm. As we also found in the other reactions of diphenyl disulfide, the irradiation with the light of 450 nm provided the best yields[18]. We speculated that the energy provided by the light of 450 nm is appropriate for the break of the S-S bond. The light of shorter wavelengths provides too much energy to cause the side reactions. On the other hand, the light of longer wavelengths cannot provide the enough energy to break the S-S bond.

A tentative reaction mechanism is outlined in Scheme 3. The diphenyl disulfide is firstly activated under the photoirradiation. A single electron transfer from iodide to the activated diphenyl disulfide provides a diphenyl disulfide anion radical **A.** The fragmentation of **A** generates a thiophenol anion and a phenylthiyl radical **B**. The coupling of iodine radical and **B** gives arylsulfenyl iodine **C**. The subsequent electrophilic substitution with the indole affords the 3-arylthioindole product[12].



Scheme 3. Proposed reaction mechanism.

In summary, we have developed a visible-light promoted synthesis of 3-arylthioindoles from indoles and diaryl disulfides. The reaction can be promoted by the catalytic amount of sodium iodide. A series of 3-arylthioindoles were prepared in good yields. The reaction is suggested to occur via electrophilic arylsulfenyl iodine intermediates, which are formed after the photo promoted single electron transfer from iodide to diphenyl disulfides. The finding provides a practical strategy for the synthesis of 3-arylthioindoles.

Acknowledgments

We thank the National Natural Science Foundation of China (no. 21472248) for the financial support of this study.

Supplementary Material

Supplementary data associated with this article can be found in the online version, at http://. These data include experimental procedure, characterization data of products, UV-vis spectra, ^{1}H and ^{13}C NMR spectra.

References and notes

1. (a) Chripkova, M.; Zigo, F.; Mojzis, J. *Molecules*, **2016**, *21*, 1626. (b) Walton, K.; Berry, J. P. *Mar. drugs*, **2016**, *14*, 73. (c) Sunil, D.; R Kamath, P. *Mini Rev. Med. Chem.*, **2016**, *16*, 1470. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.*, **2006**, *106*, 2875. (e) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.*, **2009**, *48*, 9608.
2. (a) La Regina, G.; Edler, M. C.; Brancale, A.; Kandil, S.; Coluccia, A.; Piscitelli, F.; Scovassi, A. I. *J. Med. Chem.*, **2007**, *50*, 2865. (b) De Martino, G.; La Regina, G.; Coluccia, A.; Edler, M. C.; Barbera, M. C.; Brancale, A.; Silvestri, R. *J. Med. Chem.*, **2004**, *47*, 6120.
3. (a) La Regina, G.; Coluccia, A.; Brancale, A.; Piscitelli, F.; Gatti, V.; Maga, G.; Novellino, E. *J. Med. Chem.*, **2011**, *54*, 1587. (b) Ragno, R.; Coluccia, A.; La Regina, G.; De Martino, G.; Piscitelli, F.; Lavecchia, A.; Maga, G. *J. Med. Chem.*, **2006**, *49*, 3172. (c) De Martino, G.; La Regina, G.; Coluccia, A.; Edler, M. C.; Barbera, M. C.; Brancale, A.; Silvestri, R. *J. Med. Chem.*, **2004**, *47*, 6120. (d) Silvestri, R.; Artico, M.; Bruno, B.; Massa, S.; Novellino, E.; Greco, G.; La Colla, P. *AntiVir. Chem. Chemoth.*, ***1998***, *9*, 139.
4. Unangst, P. C.; Connor, D. T.; Stabler, S. R.; Weikert, R. J.; Carethers, M. E.; Kennedy, J. A.; Conroy, M. C. *J. Med. Chem.*, **1989**, *32*, 1360.
5. Funk, C. D. *Nat. Rev. Drug Discovery*, **2005**, *4*, 664.
6. (a) Equbal, D.; Lavekar, A. G.; Sinha, A. K. *Org. Biomol. Chem.*, **2016**, *14*, 6111. (b) Yi, S. L.; Li, M. C.; Mo, W. M.; Hu, X. Q.; Hu, B. X.; Sun, N.; Jin, L. Q.; Shen, Z. L. *Tetrahedron Lett.*, **2016**, *57*, 1912. (c) He, Y. Q.; Liu, S. K.; Wen, P.; Tian, W. F.; Ren, X. Y.; Zhou, Q. X.; Ma, H. J.; Huang, G. *ChemistrySelect*, **2016**, *1*, 1567. (d) Liu, X. X.; Cui, H. H.; Yang, D. S.; Dai, S. C.; Zhang, G. Q.; Wei, W.; Wang, H. *Catal. Lett.*, **2016**, *146*, 1743. (e) Zhang, H. L.; Bao, X. Z.; Song, Y. M.; Qu, J. P.; Wang, B. M. *Tetrahedron*, **2015**, *71*, 8885. (f) Liu, Y. Y.; Zhang, Y.; Hu, C. F.; Wan, J. P.; Wen, C. P. *RSC Adv.*, **2014**, *4*, 35528. (g) Yadav, J. S.; Reddy, B. V. S.; Reddy, Y. J.; Praneeth, K. *Synthesis*, **2009**, *9*, 1520. (h) Yadav, J. S.; Reddy, B. S.; Reddy, Y. J. *Tetrahedron Lett.*, **2007**, *48*, 7034. (i) Maeda, Y.; Koyabu, M.; Nishimura, T.; Uemura, S. *J. Org. Chem.*, **2004**, *69*, 7688. (k) Schlosser, K. M.; Krasutsky, A. P.; Hamilton, H. W.; Reed, J. E.; Sexton, K. *Org. Lett.*, **2004**, *6*, 819. (l) Campbell, J. A.; Broka, C. A.; Gong, L.; Walker, K. A.; Wang, J. H. *Tetrahedron lett.*, **2004**, *45*, 4073.
7. (a) Wu, Q.; Zhao, D. B.; Qin, X. R.; Lan, J. B.; You, J. S. *Chem. Commun.*, **2011**, *47*, 9188. (b) Hamel, P. *J. Org. Chem.*, **2002**, *67*, 2854. (c) Raban, M.; Chern, L. J. *J. Org. Chem.*, **1980**, *45*, 1688.
8. (a) Rahaman, R.; Barman, P. *Synlett*, **2017**, *28*, 684. (b) Yang, Y., Zhang, S., Tang, L., Hu, Y. B., Zha, Z. G.; Wang, Z. Y. *Green Chem.*, **2016**, *18*, 2609. (c) Rahaman, R., Devi, N.; Sarma, K.; Barman, P. *RSC Adv.*, **2016**, *6*, 10873. (d) Nookaraju, U.; Begari, E.; Yetra, R. R.; Kumar, P. *ChemistrySelect*, **2016**, *1*, 81. (e) Zhao, W. N.; Xie, P.; Bian, Z. G.; Zhou, A. H.; Ge, H. B.; Zhang, M.; Ding, Y. C.; Zheng, L. *J. Org. Chem.*, **2015**, *80*, 9167. (f) Li, X. W.; Xu, Y. L.; Wu, W. Q.; Jiang, C.; Qi, C. R.; Jiang, H. F. *Chem. Eur. J.*, **2014**, *20*, 7911. (g) Kumaraswamy, G.; Raju, R. *Adv. Synth. Catal.*, **2014**, *356*, 2591. (h) Yang, F. L.; Tian, S. K. *Angew. Chem. Int. Ed.*, **2013**, *52*, 4929.
9. (a) Marcantoni, E.; Cipolletti, R.; Marsili, L.; Menichetti, S.; Properzi, R.; Viglianisi, C. *Eur. J. Org. Chem.*, **2013**, *1*, 132. (b) Silveira, C. C.; Mendes, S. R.; Wolf, L.; Martins, G. M. *Tetrahedron Lett.*, **2010**, *51*, 2014. (c) Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G. R. *Org. Lett.*, **2006**, *8*, 565.
10. Jain, S.; Shukla, K.; Mukhopadhyay, A.; Suryawanshi, S. N.; Bhakuni, D. S. *Synth. Commun.*, **1990**, *20*, 1315.
11. (a) Fang, X. L.; Tang, R. Y.; Zhong, P.; Li, J. H. *Synthesis*, **2009**, *24*, 4183. (b) Li, Z.; Hong, J. Q.; Zhou, X. G. *Tetrahedron*, **2011**, *67*, 3690.
12. (a) Ge, W. L.; Wei, Y. Y. *Green Chem.*, **2012**, *14*, 2066. (b) Chen, S. Q.; Wang, Q. M.; Xu, P. C.; Ge, S. P.; Zhong, P.; Zhang, X. H. *Phosphorus, Sulfur, and Silicon*, **2016**, *191*, 100.
13. (a) Huang, D. Y.; Chen, J. X.; Dan, W. X.; Ding, J. C.; Liu, M. C.; Wu, H. Y. *Adv. Synth. Catal.*, **2012**, *354*, 2123. (b) Silveira, C. C.; Mendes, S. R.; Wolf, L.; Martins, G. M.; von Mühlen, L. *Tetrahedron*, **2012**, *68*, 10464. (c) Prasad, C. D.; Kumar, S.; Sattar, M.; Adhikary, A.; Kumar, S. *Org. Biomol. Chem.*, **2013**, *11*, 8036. (d) Gogoi, P.; Gogoi, S. R.; Kalita, M.; Barman, P. *Synlett*, **2013**, *24*, 873.
14. (a) Gao, Z. C.; Zhu, X.; Zhang, R. H. *RSC Adv*, **2014**, *4*, 19891. (b) Sang, P.; Chen, Z. K.; Zou, J. W.; Zhang, Y. H. *Green Chem.*, **2013**, *15*, 2096. (c) Zou, L. H.; Reball, J.; Mottweiler, J.; Bolm, C. *Chem. Commun.*, **2012**, *48*, 11307. (d) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis*, **1988**, *6*, 480.
15. (a) La Regina, G.; Gatti, V.; Famiglini, V.; Piscitelli, F.; Silvestri, R. *ACS Comb. Sci.*, **2012**, *14*, 258. (b) Azeredo, J. B.; Godoi, M.; Martins, G. M.; Silveira, C. C.; Braga, A. L. *J. Org. Chem.*, **2014**, *79*, 4125. (c) Rahaman, R.; Devi, N.; Bhagawati, J. R.; Barman, P. *RSC Adv.*, **2016**, *6*, 18929.
16. Wang, P.; Tang, S.; Huang, P. F.; Lei, A. W. *Angew. Chem. Int. Ed.*, **2017**, *56*, 3009.
17. For the reviews of visible-light-promoted transformations, see: (a) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.*, **2016**, *116*, 9850. (b) Meggers, E. *Chem. Commun.*, **2015**, *51*, 3290. (c) Hammond, G. B.; Angnes, R. A.; Li, Z.; Correia, C. R. *Org. Biomol. Chem.*, **2015**, *13*, 9152.
18. (a) Ye, L. M.; Qian, L.; Chen, Y. Y.; Zhang, X. J.; Yan, M. *Org. Biomol. Chem.*, **2017**, *15*, 550. (b) Ye, L. M.; Chen, J.; Mao, P.; Mao, Z. F.; Zhang, X. J.; Yan, M. *Tetrahedron Lett.*, **2017**, *58*, 874.
19. The exact reason for the result is not clear so far. We speculated that the by-product thiophenol can be oxidized to diphenyl disulfide by oxygen under photoirradiation (see Kim, J. H.; Yoon, J. L.; Yoon, S. *J. Phys. Chem. A*, **2010**, *114*, 12010). Small amount of oxygen is helpful for increasing the yield. Because the reaction proceeds via a radical pathway, high oxygen concentration can inhibit the radical

process and lead to a low yield.

Highlights

- An efficient and convenient synthesis of 3-arylthioindoles from indoles and diaryl disulfides via visible-light irradiation.
- Sodium iodide was used as the catalyst.
- A variety of indoles and diaryl disulfides are applicable.

Graphical Abstract

Visible-light promoted synthesis of 3-arylthioindoles from indoles and diaryl disulfides

Lin-miao Ye, Jie Chen, Peng Mao, Xue-jing Zhang and Ming Yan*

Leave this area blank for abstract info.