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Visible-Light-Driven Thiol-yne Reaction: A Practical Synthesis of (1,2-diarylvinyl)(aryl/alkyl)sulfides

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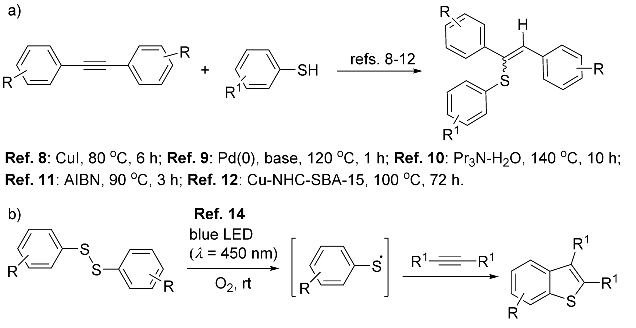
A mild, efficient and straightforward visible-light-driven method has been developed to construct 1,2-diarylvinyl sulfides under catalyst- and additive-free conditions. The formation of small amounts of thiyl radicals under visible light irradiation allows the synthesis of 1,2-diarylvinyl sulfides in good yield with an excellent functional group tolerance.

The addition of thiols to alkynes is one of the most straightforward methods for obtaining vinyl sulfides used as a potential building block for the synthesis of many polymeric materials, natural products and synthetic reagents. Usually thiols add to terminal alkynes under radical conditions to afford anti-Markovnikov type vinyl sulfides with excellent regioselectivity, but as mixture of geometric isomers. This thiol-yne reaction (also known as alkyne hydrothiolation) is accepted as a click chemistry reaction and largely utilized in polymer chemistry,[1–2] material science,[3] peptide and protein labelling.[4–5] Several synthetic strategies are reported for the hydrothiolation of terminal alkynes under free-radical and metal-catalysed conditions.[1,6–7] Nevertheless, only a handful of examples (Scheme 1a) address the direct functionalization of 1,2-disubstituted alkynes by thiols.[8–12] This is due to the lower chemical stability of 1,2-disubstituted alkynes, in particular 1,2-diarylalkynes, against Brønsted- and Lewis acids, heat and UV-light. For example, in the presence of catalytic amounts of either triflic acid or $TaCl_5$,[13–15] 1,2-diarylacetylenes react to poly-(buta-1,3-diene-1,2,3,4-tetraarenes). So, the development of mild reaction conditions using diarylacetylenes as a starting material is in demand.

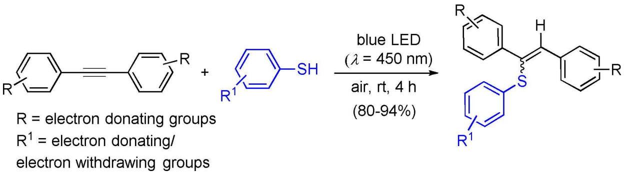


Ref. 8: CuI, 80 °C, 6 h; **Ref. 9**: Pd(0), base, 120 °C, 1 h; **Ref. 10**: Pr_3N-H_2O, 140 °C, 10 h; **Ref. 11**: AIBN, 90 °C, 3 h; **Ref. 12**: Cu-NHC-SBA-15, 100 °C, 72 h.

Scheme 1. Radical thiol-yne reaction.

Visible-light-mediated photoredox catalysis has been established as an attractive alternative to traditional methods of generating radical intermediates under mild conditions.[16–17] In 2017, Yan and co-workers showed that arylthiyl radicals (Scheme 1b) can be generated through the homolytic cleavage of the diphenyl disulfide under irradiation (blue LED, λ = 450 nm).[18] The authors prepared a series of benzothiophenes bearing ester, ketone, aldehyde and aryl substituents from readily available disulfides and alkynes with the protocol, cf. Scheme 1b. In the same year, Wang and co-workers utilized the same approach for the synthesis of 2,3-diarylbenzothiophenes from 1,2-diarylalkynes and a stoichiometric amount of disulfides.[19] Based on these reports, we hypothesized that the use of catalytic amounts of disulfides in the presence of a thiol would provide (1,2-diarylvinyl)(aryl/alkyl)sulfides under mild conditions. Moreover, thiols are known to undergo air oxidation to form disulfides under ambient conditions, which will ensure the formation of (1,2-diarylvinyl)(aryl/alkyl)sulfides without external addition of disulfides as a radical carrier.

Herein we demonstrate a catalyst- and additive-free, operationally simple protocol for the synthesis of a series of vinyl sulfides from diarylalkynes and thiols via visible light (blue LEDs: $h\nu = 455 \pm 5$ nm) promoted reaction (Scheme 2). Mono-addition occurs almost exclusively with no bis-adduct being formed under these conditions. Moreover, all reactions proceeded under ambient conditions and pure products were



Scheme 2. Visible-light-induced synthesis of vinyl sulfides from diarylalkynes and thiols reported in this work.

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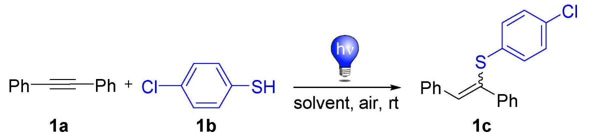
obtained readily by recrystallization or filtration through flash chromatography.

We began this study by choosing diphenylacetylene (**1 a**) and *p*-chlorothiophenol (**1 b**) as model substrates. Upon irradiation with blue light for 4 h, we observed a quantitative amount of product (**1 c**) as *cis*- and *trans*-isomers in acetonitrile (Table 1). This was further confirmed by ^1H NMR spectroscopic monitoring experiments in CD_3CN (see Figure S3 in the Supporting Information). Usually alkynes are prone to multiple additions,[11] but a clean monoaddition to vinyl sulfides has been observed without side product formation (see GC-MS and NMR in the Supporting Information). Changing the solvent or light irradiation from blue to green did not alter the reaction outcome (Table 1).

Using the optimized conditions, we investigated the scope and limitations for alkynes and thiols (Scheme 3). Both aliphatic (**11 c**–**13 c**) and aromatic thiols (**1 c**–**10 c**) with various substituents react smoothly with diphenylacetylene (**1 a**) under these reaction conditions and afforded the expected cis- and trans-isomers of 1,2-diarylvinyl sulfides in moderate to good yields. The functional group tolerance comprises halide (Cl, Br), alkyl, naphthyl, amine and CF_3. Likewise, different diarylalkynes that are prone to multiple additions in thiol-yne reactions underwent a clean monoaddition to afford vinyl sulfides (**14 c**–**19 c**) as a mixture of *cis*- and *trans*-isomers. Interestingly, unsymmetrical diaryl alkynes (**15 c**–**18 c**) gave two-sets of *cis*- and *trans*-isomers (see the Supporting Information) due to addition of sulfur to different carbon atoms. Formation of four products (see the Supporting Information) from **15 c**–**18 c** indicates that the thiol addition proceeds without regioselectivity. Thioanisole ($C_6H_5SCH_3$) and diphenylacetylene do not react under the optimized conditions even after 12 h of irradiation suggesting that a free thiol (–SH) group is essential.

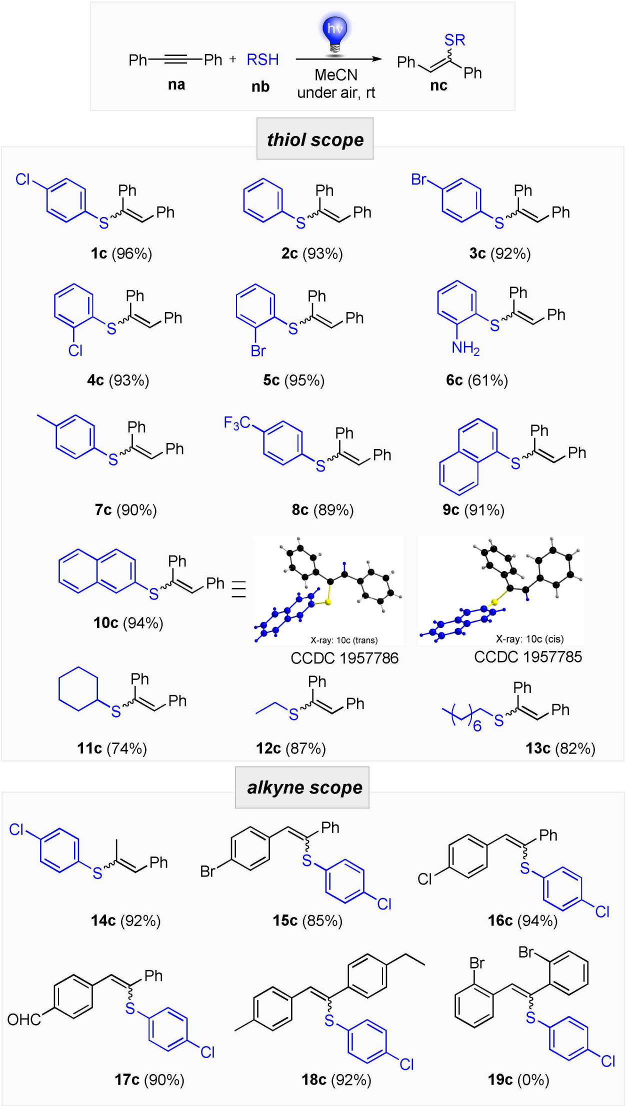
We propose that the reaction involves oxidation of thiol to disulfide (<5%) in the presence of air, followed by homolysis of the S–S bond to generate thiyl radicals. The thiyl radical adds across the alkyne and the resulting vinyl radical abstracts a hydrogen atom from an unreacted thiol compound to generate the vinyl sulfide compound (Scheme 4).

Table 1. A selected results of optimization of reaction conditions.[a]



Entry	Solvent	Time [h]	Yield [%][b]
1	MeCN	4	96
2	DCE	4	92
3	DMSO	4	58[c]
4	THF	4	87
5	Hexane	4	82
6	neat	4	69
7	toluene	4	93
8	MeCN	12	42[d]
9	MeCN	4	73[e]
10	MeCN	12	32[f]

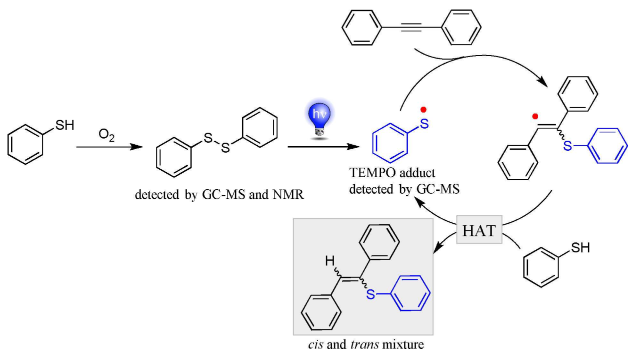
[a] The thiol **1 b** (1.0 mmol), alkyne **1 a** (1.0 mmol), solvent (2–3 mL), photoirradiation with a 5 W blue LED, room temperature and open-air atmosphere. [b] Yields were determined by GC analysis. [c] Formation of benzothiophene (>30%) observed. [d] Green light irradiation. [e] Under N_2. [f] No light.



Scheme 3. Substrate scope. [a] Reaction conditions: **na** (1.0 mmol), **nb** (1.0 mmol), CH_3CN (2–3 mL), photoirradiation with a 5 W blue LED for 4 h, room temperature and open-air atmosphere. [b] Isolated yields.

Disulfides can exist as an impurity in the thiols or are readily formed by aerial oxidation. We detected disulfides by NMR and GC-MS analysis under the experimental conditions (see: Figures S1 and S2 in the Supporting Information). A direct homolytic cleavage of S–S bond under visible light irradiation is well-known in the literature.[20–21] Reactions in the presence of TEMPO confirmed the formation of thiyl radicals (GC-MS, Figure S23). The vinyl radical could likely not be trapped by TEMPO due to a fast HAT process. Reaction quantum yield measurement ($\Phi_{reaction} = 118\%$) are in agreement with the proposed radical chain mechanism.[22]

In summary, we have shown that radical thiol-yne reactions can be photoinitiated upon direct irradiation with visible light in the absence of a photocatalyst. The products are obtained in



Scheme 4. Plausible mechanism.

high yield and a variety of diarylalkynes and 1-phenyl-1-propyne react with aliphatic- and aromatic thiols. Previously reported protocols for the functionalization of 1,2-diarylalkynes by thiols require a radical initiator, bases, elevated temperature or transition metal complexes limiting their application, e.g. in bio-conjugation.[23] The use of UV light may also cause undesired radical decomposition in polymer applications.[24] This protocol aims to overcome such limitations in part.

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Keywords: alkynes · catalyst-free · radical reactions · thiol-yne · vinyl sulfides

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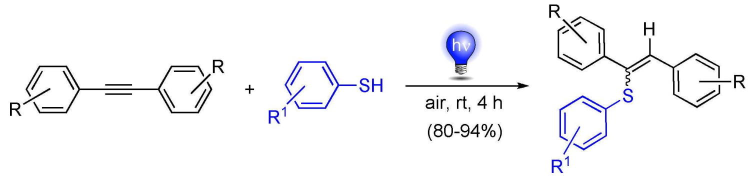

Quick and easy: A mild and efficient visible-light-mediated synthesis of 1,2-diarylvinyl sulfides under catalyst- and additive-free conditions is reported. The reaction proceeds with excellent functional group tolerance.

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