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Letter

Photocatalyst- and Transition-Metal-Free Visible-Light-Promoted Intramolecular C(sp^2)−S Formation

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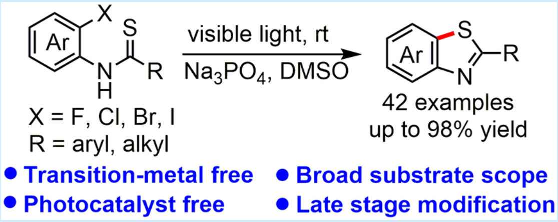
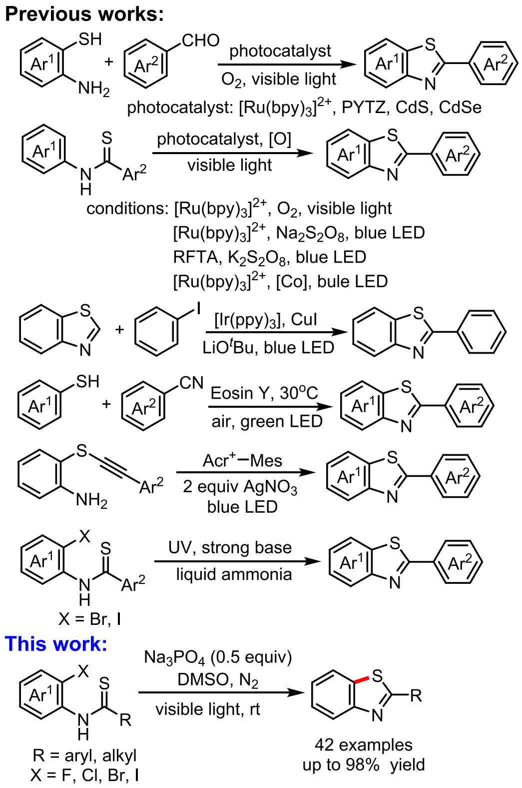
ABSTRACT: A photocatalyst- and transition-metal-free visible-light-induced cyclization of *ortho*-halothiobenzanilides has been developed. Upon irradiation with visible light, substrates undergo dehalogenative cyclization to 2-aryl benzothiazoles with high efficiency and selectivity. This photocyclization exhibits a high tolerance to various functional groups, is applicable for the synthesis of 2-alkyl benzothiazoles, and is easy to set up for gram-scale reaction.



As in the past years, visible-light photoredox catalysis has become an efficient protocol to forge C−C, C−O, C−N, and C−S bonds.[1,2] Most of the visible-light-induced conversions require the use of exogenous photosensitizers (e.g., polypyridyl Ru/Ir complexes or organic dyes) because common organic molecules do not absorb light in the visible region.[3,4] In recent years, noncovalent interaction of electron donor−acceptor (EDA) complexes can mediate photocatalyst-free transformations under visible light.[5−9] However, the direct visible-light irradiation of donor−acceptor complexes to induce intramolecular cross couplings remains underexplored in the absence of photoredox catalysts.

2-Aryl benzothiazoles are common building blocks found in pharmaceuticals, natural products, agrochemical complexes, and functional materials.[10] Consequently, their synthesis has attracted much attention (Scheme 1).[11−16] Apart from thermal reactions,[17,18] visible-light-triggered construction of 2-aryl benzothiazoles, including (i) oxidative condensation of 2-aminothiophenols with aromatic aldehydes,[19,20] (ii) intramolecular C(sp^2)−H thiolation of thiobenzanilides,[21] (iii) Cu-catalyzed C−H arylation of benzothiazole with iodobenzene,[22] (iv) oxidative coupling of thiophenols and arylnitriles,[23] and (v) thia−Wolff rearrangement of alkynyl sulfide,[24] have been developed. The above photoreactions necessitate expensive or/and toxic photoredox catalysts such as [Ru(bpy)$_3$]$^{2+}$ and [Ir(ppy)$_3$], which play a key role in the formation of benzothiazoles but may contaminate the final products. Using a photocatalyst-free strategy could be an efficient alternative to avoid their cost, toxicity, and contamination. Ultraviolet (UV)-light-induced intramolecular aromatic substitutions of 2-bromo/iodo-thiobenzanilides to benzothiazoles with a strong base in liquid ammonia were reported.[25] The application of high-energy UV light and harsh conditions limits the substrate scope and causes unwanted side reactions. Herein, we reported the visible-light-induced dehalogenative cyclization of 2-halothiobenzanilides into benzothiazoles at

Scheme 1. Photosynthesis of 2-Aryl Benzothiazoles



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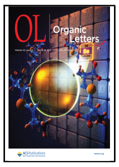
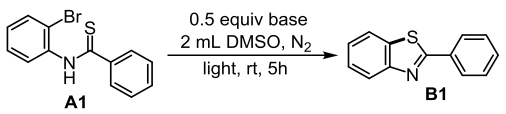


ambient temperature. Notably, these reactions avoid the use of an external photosensitizer and transition-metal catalyst typically required to effect C−S cross couplings.[26]

In 2017, Miyake et al. developed a visible-light-promoted protocol for C(sp^2)−S cross coupling of thiols and aryl halides via intermolecular charge transfer without photoredox catalysts and transition-metal catalysts.[27] Very recently, we found that thiobenzanilide derivatives can absorb visible light, and their photoexcited states undergo cyclization to benzothiazoles using stoichiometric 2,2,6,6-tetramethylpiperidine *N*-oxyl as the hydrogen atom transfer reagent.[28] The oxidative conversion required a relatively expensive oxidant and displayed low positional selectivity. For *meta*-substituted thioanilides, a mixture of two regioisomers was formed. These above results stimulated us to explore the direct visible-light irradiation of *ortho*-halothiobenzanilides into 2-aryl benzothiazole through intramolecular electron transfer under catalyst-free conditions.

We initially chose *N*-(2-bromophenyl)benzothioamide (**A1**) as the model substrate to optimize reaction conditions (Tables 1 and S1). The irradiation of **A1** with Na_3PO_4 in DMSO was carried out under visible light from a 45 W compact fluorescent lamp (CFL) (Figure S1). Pleasingly, after 5 h of CFL irradiation, we isolated the desired product 2-phenylbenzo[d]thiazole (**B1**) in 99% HPLC assay yield (entry 1; HPLC = high performance liquid chromatography) with high selectivity. A series of bases (e.g., $KHCO_3$, NaOAc, Na_2HPO_4, Na_2CO_3, K_2CO_3, KOH, NaOH, Et_3N, and (i-Pr)$_2$EtN) were screened (entries 2−10). Na_3PO_4, KOH, and NaOH are excellent bases for this transformation (entries 1, 7, and 8). Good conversions were observed using others. We obtained lower yield (91%), as the Na_3PO_4 loading was decreased from 0.5 equiv to 0.2 equiv (Table S1, entry 1). The reaction proceeded in 76% yield in the absence of base (Table S1, entry 2). The process was largely sensitive to the used solvent (Table S1, entries 3−10). DSMO was the optimal solvent (entry 1). DMF, MeOH, and EtOH were less effective than DMSO. MeCN, THF, or 1,4-dioxane offered 15−39% yield of **B1**. Only a trace of products was observed when the reaction was carried out in CH_2Cl_2 or toluene. Gratifyingly, high product yield (98%) was obtained after 5 h of sunlight irradiation (entry 12). No desired product was formed in the dark (entry 13), displaying that visible-light irradiation was essential for this debrominative cyclization. The reaction was performed in air to afford the desired product **B1** in 61% yield and a desulfurizated product *N*-(2-bromophenyl)benzamide in 17% yield (entry 14). Thus, the optimized conditions were found to be 50 mol % of Na_3PO_4 as base and DMSO as solvent under the irradiation of visible light at ambient temperature. Notably, this photocyclization proceeded effectively without the addition of transition metal and photoredox catalyst.

Table 1. Parameters for Intramolecular Cyclization[a]

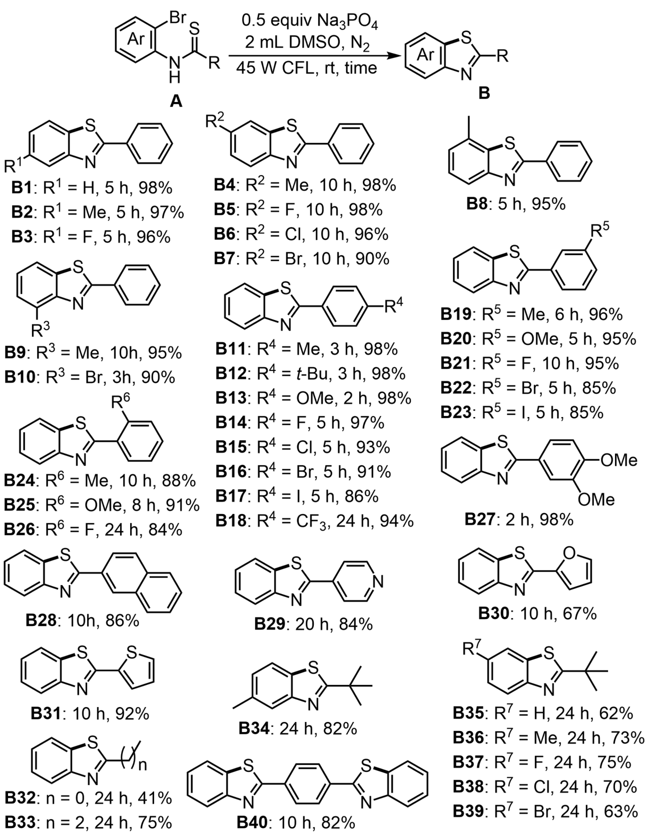


entry	base	conversion (%)	yield (%)
1	Na_3PO_4	>99	99
2	$KHCO_3$	99	89
3	NaOAc	99	88
4	Na_2HPO_4	>99	94
5	Na_2CO_3	99	86
6	K_2CO_3	99	88
7	KOH	>99	99
8	NaOH	>99	99
9	Et_3N	92	87
10	(*i*-Pr)$_2$EtN	93	88
11		92	76
12[b]	Na_3PO_4	>99	98
13[c]	Na_3PO_4	8	0
14[d]	Na_3PO_4	84	61

[a] Reaction conditions: **A1** (0.2 mmol), Na_3PO_4 (0.1 mmol, 0.5 equiv), DMSO (2 mL), N_2, irradiation under a 45 W CFL for 5 h with cooling by a fan, HPLC assay conversion, and yield. [b] Under sunlight (the maximum power density is about 5 mW cm^{-2}). [c] In the dark. [d] In air, *N*-(2-bromophenyl)benzamide was formed in 17% yield.

After determining the optimized reaction conditions (Table 1, entry 1), we explored the photocyclization of other substrates with an *ortho* C(sp^2)−Br bond. As shown in Scheme 2, a range of *N*-(2-bromophenyl)benzothioamides with electron-donating or electron-withdrawing substituents on the 3-, 4-, 5-, or 6- position of *N*-phenyl rings were compatible to afford the corresponding 2-aryl benzothiazoles **B1**−**B10** in high yields (90−98%) after the 3−10 h irradiation. The photocyclization of *N*-(2-bromophenyl)benzothioamide derivatives bearing various 2-aryl groups was also investigated (**B11**−**B31**). The electronic and steric effects of substituents on the 2-aryl ring affect product outcomes. Sterically encumbered benzothioamides with methyl, methoxyl, and fluoride groups at

Scheme 2. Synthesis of 2-Substituted Benzothiazoles[a]

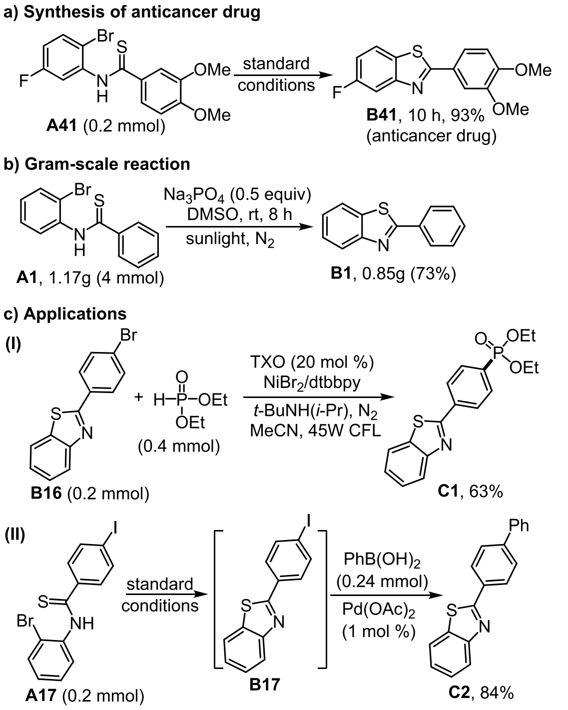


[a] Reaction condition: **A** (0.2 mmol), Na_3PO_4 (0.1 mmol, 0.5 equiv), DMSO (2 mL), N_2, irradiation of 45 W CFL, and isolated yields.

the *ortho* position of the 2-phenyl ring (**B24**−**B26**) showed lower activities than the corresponding ones bearing groups on the 3- and 4-postion (**B11**, **B13**−**B14**, and **B19**−**B21**). The reaction was performed with substrates bearing electron-donating substituents at the p-position of the 2-aryl ring with excellent yield (98% for **B11**−**B13**) after 2−3 h of CFL irradiation. Electron-deficient 2-aryls with F, Cl, Br, I, or CF$_3$ at the 4-position were also tolerated in this photocyclization process, but extended irradiation time (5 or 24 h) was necessary to reach 86−94% yields (**B14**−**B18**). To our delight, benzothioamides with other halo groups (F, Cl, Br, and I), which have proven to be challenging substrates using other reaction conditions, readily underwent debrominative cyclization to deliver halogenated products (**B14**−**B17**, **B21**−**B23**, and **B26**), facilitating further functionalization of products. The optimized conditions were also suitable for *N*-(2-bromophenyl)-3,4-dimethoxybenzothioamide and *N*-(2-bromophenyl)naphthalene-2-carbothioamide to provide the expected products **B27** and **B28** in 80−98% yields. Substrates **A29**−**A31** bearing the pyridine, furan, or thiophene moiety were converted to **B29**−**B31** in 67−92% yields. *N*-(2-Bromophenyl)alkanethioamides **A32**−**A39** were also found to be the competent substrates for this photocyclization, producing the corresponding products 2-alkylbenzothiazoles **B32**−**B39** in moderate to good yields. N^1,N^4-Bis(2-bromophenyl)benzene-1,4-bis(carbothioamide) **A40** underwent the double-cyclization reaction in one step to give **B40** in 82% yield under standard reaction conditions.

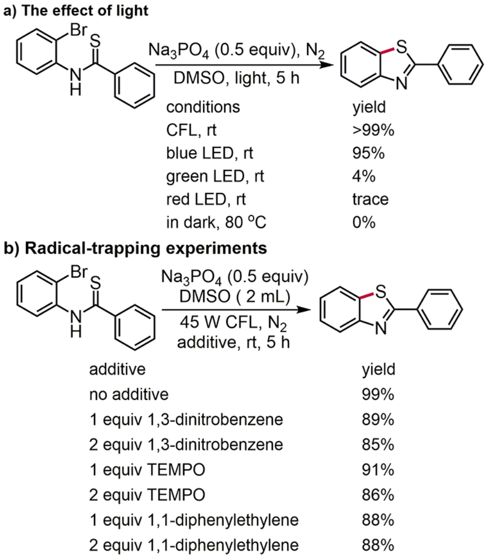
With an extensive exploration of the scope of substrates, we turned our attention to the applications of this catalyst-free photoreaction (Scheme 3). The cyclization of *N*-(2-bromo-5-fluorophenyl)-3,4-dimethoxybenzothioamide **A41** afforded 2-(3,4-dimethoxyphenyl)-5-fluorobenzo[d]thiazole **B41** as a potent antitumor agent, which avoids transition-metal contamination (Scheme 3a). A gram-scale reaction of **A1** (1.17 g, 4 mmol) was performed to deliver **B1** in 73% yield (0.85 g) under natural sunlight for 8 h (Scheme 3b, see the Supporting Information). Moreover, we explored some synthetic applications of this photocyclization protocol. The cross coupling of 2-(4-bromophenyl)-benzo[d]thiazole (**B16**) with diethyl phosphonate by thioxanthen-9-one/(dtbbpy)-NiBr$_2$ (dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) dual catalysis under visible light yielded calcium antagonist diethyl(4-(benzo[d]thiazol-2-yl)phenyl)-phosphonate (**C1**) with good yield (Scheme 3c(I) and see the Supporting Information). Due to this simple photochemical reaction system, it is possible to dispense with a workup and isolation procedure before carrying out further derivatization of the produced benzothiazole compounds. For example, PhB(OH)$_2$ and a catalytic amount of Pd(OAc)$_2$ were added to the same reaction flask after the photoirradiation of **A17** for 5 h, and the resulting mixture was heated at 110 °C for 5 h. 2-([1,1′-Biphenyl]-4-yl)benzo[d]thiazole (**C2**) was isolated in 84% yield (Scheme 3c(II)).

Scheme 3. Gram-Scale Reaction and Applications



The UV/vis absorption spectra of some substrates were recorded at room temperature (Figure S2). The absorption spectra of **A1**, **A4**, **A14**, **A24**, **A28**, **A31**, **A35**, and **A41** in DMSO each indicated the absorption range from UV to visible wavelengths with the absorption edge at about 450−500 nm. The cyclization of **A1** was carried out upon the irradiation of CFL, and blue LED, green LED, and red LED afforded **B1** in 99%, 95%, 4%, and trace yields, respectively (Scheme 4).

Scheme 4. Control Experiments



a) The effect of light

conditions	yield
CFL, rt	>99%
blue LED, rt	95%
green LED, rt	4%
red LED, rt	trace
in dark, 80 °C	0%

b) Radical-trapping experiments

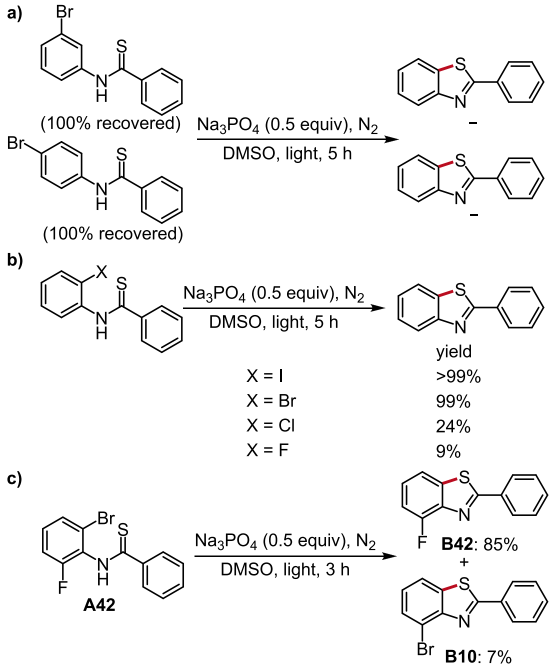
additive	yield
no additive	99%
1 equiv 1,3-dinitrobenzene	89%
2 equiv 1,3-dinitrobenzene	85%
1 equiv TEMPO	91%
2 equiv TEMPO	86%
1 equiv 1,1-diphenylethylene	88%
2 equiv 1,1-diphenylethylene	88%

These yields are correlated with the spectral overlap between the emission of radiation light and the absorbance of **A1** (Figure S3). As depicted in Figure S4, the cyclization progressed smoothly under the CFL irradiation, but no further transformation was observed when the light source was moved away. Even when heated at 80 °C, no desired product was detected in the dark. These above results confirmed that this present intramolecular cyclization was a photochemical process.

To further elucidate the mechanism of this reaction, several control experiments were conducted. When 1,3-dinitrobenzene as a strong electron acceptor was added into the photoreaction system, inhibition of the cyclization was not observed (Scheme

4). An intermolecular electron transfer process was ruled out. We also studied the effect of radical inhibitors on this photoreaction. The addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the model reaction hardly suppressed the cyclization. The reaction could be performed in the presence of 1,1-diphenylethylene without a significant loss of yield of **B1**. Under the standard conditions, *N*-(3-bromophenyl)benzothioamide or *N*-(4-bromophenyl)benzothioamide did not undergo photocyclization to **B1** or cross coupling (Scheme 5a). These results display that no aryl free radicals are involved in the reaction process.

Scheme 5. Reactivity of Different Halogenated Substrates

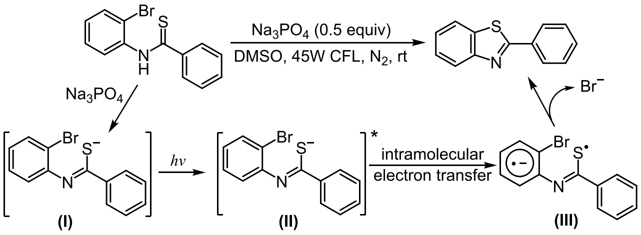


The oxidative cyclization of **A1** over time was monitored using HPLC (Figure S5). Product **B1** got accumulated at the same rate as the consumption of **A1**. Substrate **A1** was totally converted in 4 h. A plot of the percentage of residual substrate (c/c_0) with irradiation time (t) showed that the kinetics of this reaction obeyed a zero-order rate law. The conversions of **A1** and its iodo, chloro, and fluoro derivatives into **B1** were also monitored over time using HPLC as shown in Figure S6. The order of reactivity was *N*-(2-iodophenyl)benzothioamide > **A1** > *N*-(2-chlorophenyl)benzothioamide > *N*-(2-fluorophenyl)-benzothioamide. *N*-(2-Bromo-6-fluorophenyl)benzothioamide **A42** afforded a mixture of 4-fluoro-2-phenylbenzothiazole **B42** (85%) and 4-bromo-2-phenylbenzothiazole **B10** (7%) (Scheme 5c). The yield of two isomers is consistent with the halogen activity.

This C–S cross coupling photoreaction was also investigated through density functional theory (DFT) calculations. The molecular geometry was optimized using the DFT method of wB97XD with the basis set of def2-tzvp (see Supporting Information). The activation barriers of iodo, bromo, and chloro derivatives are 30.7, 31.8, and 33.3 kcal mol^{-1}, respectively, which are in agreement with the experimental results.

On the basis of the above results and evidence, a plausible mechanism for this visible-light-induced intramolecular C(sp^2)–S cross coupling is proposed (Scheme 6). Substrate **I** or its anion accepts a photon to generate its excited state **II**. The species **II** then undergoes an intramolecular electron transfer from the thiolate anion to the *N*-aryl ring, forming **III** possessing the thiyl free radical and aryl halide radical anion. The intermediate **III** undergoes debrominative cyclization to give the desired product.

Scheme 6. Proposed Mechanism



In summary, we have developed a highly efficient method for visible-light-promoted intramolecular C(sp^2)–S bond formation in the absence of a photosensitizer and transition metal catalyst. Under the irradiation of compact fluorescent lamp light, blue LED, or natural sunlight, 2-halothiobenzanilide derivatives undergo smoothly intramolecular cross coupling into 2-aryl benzothiazoles through photon absorption, electron transfer, and dehalogenative cyclization. Such a photoreaction has a broad substrate scope, proceeds efficiently on a gram scale, and is applicable to the synthesis of 2-alkyl benzothiazoles. It is anticipated that the photocatalyst- and transition-metal-free methodology may be applied to forge carbon–carbon/heteroatom bonds under visible light. These studies are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00235.

Experimental procedures, ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra, and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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