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## Visible-light-promoted synthesis of benzothiazoles from 2-aminothiophenols and aldehydes

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### ABSTRACT

A visible-light-promoted synthesis of benzothiazoles from 2-aminothiophenols and aldehydes has been developed. A wide range of aromatic, heteroaromatic and aliphatic aldehydes were successfully applied. The benzothiazole products were prepared in good yields. The reaction was carried out in the absence of transition-metal catalysts and extra additives. A radical reaction pathway was proposed.

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Benzothiazoles are an important class of heterocyclic compounds. They possess various attracting biological and pharmacological properties<sup>1</sup>, such as antimicrobial<sup>2</sup>, antitumor<sup>3</sup>, anticonvulsant<sup>4</sup> and antidiabetic<sup>5</sup> activities. A number of synthetic methods of benzothiazoles have been developed.<sup>6</sup> Among them, the condensation of 2-aminothiophenols with aldehydes is the most commonly used method. Generally, metal catalysts<sup>7</sup>, Brønsted acid catalysts<sup>8</sup>, and oxidants<sup>9</sup> are required to promote the reaction. Aminoxyl radical/oxygen<sup>10</sup> and activated-carbon/oxygen system<sup>11</sup> were also efficient for the condensation of 2-aminothiophenols and aldehydes under high temperature. Chen and co-workers found that Montmorillonite K-10 can catalyze the transformation with continuous bubbling of air.<sup>12</sup> Microwave is also used to accelerate the formation of benzothiazoles.<sup>13</sup> Recently, Han and co-workers reported an efficient synthesis of 2-arylbenzothiazoles under DMSO/air conditions, however aliphatic aldehydes are not compatible in the reaction.<sup>14</sup>

In recent years, visible-light promoted transformations have received great attentions.<sup>15</sup> The methods are cleaner, safer and more cost-effective. It was known that diphenyl disulfides can be homolytically cleaved to phenylthiyl radicals under photoirradiation.<sup>16</sup> Recently, we found that visible-light can promote the formation of benzothiazoles from diphenyl disulfides and aldehydes. The generation of phenylthiyl radicals via visible light-promoted homolysis of diphenyl disulfides is suggested as the crucial initiation step.<sup>17</sup> In 2010, Yoon and co-workers reported that visible-light directly promotes the formation of diphenyl disulfides from thiophenols in the absence

of extra catalysts or additives.<sup>18</sup> We speculate that the reaction of 2-aminothiophenols and aldehydes under visible-light irradiation can provide benzothiazoles via in situ formation and homolysis of diphenyl disulfide intermediates. Herein we report the experiment results along with this idea.

To test our hypothesis, a solution of 2-aminothiophenol and benzaldehyde in toluene was irradiated with a 12W blue LED for 6 h under an air atmosphere. To our delight, the benzothiazole **3a** was obtained in a 67% yield. The reaction conditions were further examined and the results are summarized in Table 1. Among the tested reaction solvents, ethyl acetate afforded the best yield (Table 1, entry 3). The lights of other wavelengths (254 nm, 365 nm and 530 nm) were also evaluated, but lower yields were obtained (Table 1, entries 10-12). Lower yields were observed under argon or oxygen atmosphere (Table 1, entries 13-14). The result implicated that the presence of oxygen is crucial for the reaction, but the concentration of oxygen must be controlled at a suitable scope to avoid the inhibition of the radical process. A small amount of the product was obtained when the reaction was performed in the dark (Table 1, entry 15).

**Table 1.** Screening of reaction conditions.<sup>a</sup>

Entry	Solvent	Light source	Yield (%) <sup>b</sup>
1	Toluene	450 nm	67
2	MeCN	450 nm	41

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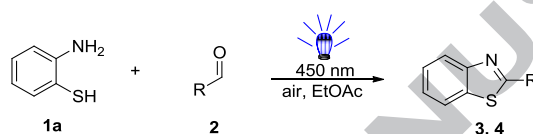
## Tetrahedron Letters

3	EtOAc	450 nm	94 (91) <sup>c</sup>
4	DCM	450 nm	51
5	DMSO	450 nm	49
6	EtOH	450 nm	79
7	AcOH	450 nm	89
8	THF	450 nm	70
9	<i>n</i> -hexane	450 nm	57
10	EtOAc	254 nm	33
11	EtOAc	365 nm	45
12	EtOAc	530 nm	26
13 <sup>d</sup>	EtOAc	450 nm	20
14 <sup>e</sup>	EtOAc	450 nm	67
15 <sup>f</sup>	EtOAc	450 nm	9

<sup>a</sup> Reaction conditions: 2-aminothiophenol **1a** (0.4 mmol), benzaldehyde **2a** (0.48 mmol), solvent (2 mL), photoirradiation for 6 h with a 12w blue LED, room temperature. <sup>b</sup> GC yields with *n*-dodecane as the internal standard. <sup>c</sup> Isolated yields after the column chromatography. <sup>d</sup> Under an argon atmosphere. <sup>e</sup> Under an oxygen atmosphere. <sup>f</sup> Reaction performed in the dark.

With the optimized reaction conditions in hand, a series of aldehydes were investigated and the results are summarized in

**Table 2.** Scope of aldehydes.<sup>a,b</sup>

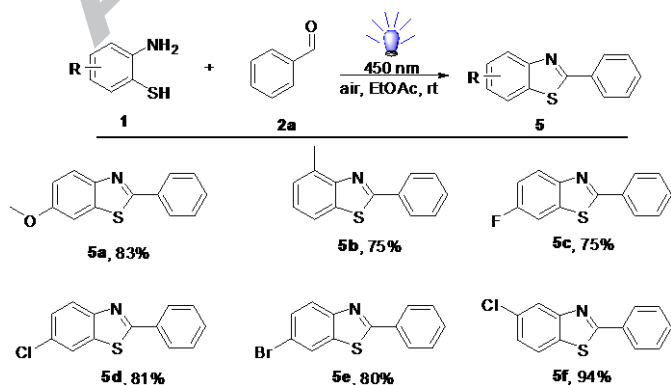


Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
1	Ph	<b>3a</b>	91	18	3-MeCOO-C <sub>6</sub> H <sub>4</sub>	<b>3r</b>	81
2	2-Me-C <sub>6</sub> H <sub>4</sub>	<b>3b</b>	85	19	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	<b>3s</b>	79
3	3-Me-C <sub>6</sub> H <sub>4</sub>	<b>3c</b>	92	20	4-AcO-C <sub>6</sub> H <sub>4</sub>	<b>3t</b>	34
4	4- <i>t</i> -Bu-C <sub>6</sub> H <sub>4</sub>	<b>3d</b>	80	21	2-furanyl	<b>3u</b>	94
5	3-MeO-C <sub>6</sub> H <sub>4</sub>	<b>3e</b>	81	22	2-thienyl	<b>3v</b>	72
6	4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>3f</b>	58	23	4'-methyl-2-pyrrolyl	<b>3w</b>	50
7	3,5-(MeO) <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>3g</b>	83	24	3-pyridinyl	<b>3x</b>	68
8	2-OH-C <sub>6</sub> H <sub>4</sub>	<b>3h</b>	83	25	4-pyridinyl	<b>3y</b>	80
9	2-F-C <sub>6</sub> H <sub>4</sub>	<b>3i</b>	83	26	3-indolyl	<b>3z</b>	77
10	2-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3j</b>	93	27	1-naphthyl	<b>4a</b>	88
11	2-Br-C <sub>6</sub> H <sub>4</sub>	<b>3k</b>	86	28	2-naphthyl	<b>4b</b>	82
12	2-I-C <sub>6</sub> H <sub>4</sub>	<b>3l</b>	71	29	<i>n</i> -propyl	<b>4c</b>	56
13	3-Br-C <sub>6</sub> H <sub>4</sub>	<b>3m</b>	91	30	cyclopropyl	<b>4d</b>	76
14	4-F-C <sub>6</sub> H <sub>4</sub>	<b>3n</b>	91	31	cyclohexyl	<b>4e</b>	60
15	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3o</b>	82	32	4-cyclohexenyl	<b>4f</b>	59
16	3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>3p</b>	86	33	benzyl	<b>4g</b>	67
17	2-Br-4-Me-C <sub>6</sub> H <sub>4</sub>	<b>3q</b>	85	34	phenylethyl	<b>4h</b>	52

<sup>a</sup> Reaction conditions: **1a** (0.4 mmol), aldehyde (0.48 mmol), EtOAc (2.0 mL), photoirradiation with a 12w blue LED, room temperature, 6-12 h. <sup>b</sup> Isolated yields.

Furthermore, we examined several substituted 2-aminothiophenols and the results are summarized in Table 3. The substitution with methoxyl, methyl, fluoro, chloro, and bromo exerted small effect on the reaction. The benzothiazoles (**5a-5f**) were obtained in good yields.

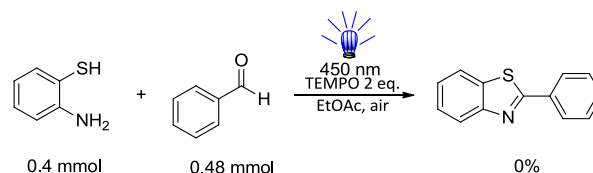
**Table 3.** Scope of 2-aminothiophenols.<sup>a,b</sup>



<sup>a</sup> Reaction conditions: 2-aminothiophenols (0.4 mmol), benzaldehyde **2a** (0.48 mmol), EtOAc (2.0 mL), photoirradiation with a 12w blue LED, room temperature, 6-12 h. <sup>b</sup> Isolated yields.

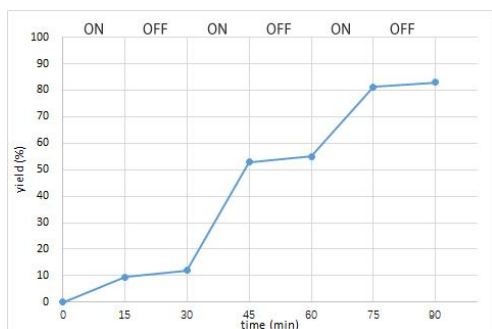
Table 2. Aromatic aldehydes bearing electron-donating groups (methyl, *tert*-butyl, methoxyl, hydroxyl) were tolerated well. The corresponding benzothiazoles (**3b-3e**, **3g**, **3h**) were obtained in good yields. The only exceptive substrate is 4-methoxybenzaldehyde, which gave a moderate yield. The substitution with halogen (F, Cl, Br, I) is also compatible. Good yields were achieved generally for **3i-3q**. Aromatic aldehydes (**2r**, **2s**) containing ester and trifluoromethyl group are also suitable substrates. The reaction of 4-acetoxy benzaldehyde delivered the product **3t** in low yield. To our delight, the reaction of heteroaromatic aldehydes such as furanyl, thienyl, pyrrolyl, pyridinyl and indolyl aldehydes gave the benzothiazoles (**3u-3z**) in moderate to good yields. More bulky 1-naphthyl and 2-naphthyl aldehydes reacted smoothly to give the products (**4a-4b**) in good yields. Moreover, a variety of aliphatic aldehydes were successfully applied. The 2-alkylbenzothiazoles (**4c-4h**) could be prepared in moderate yields.

To probe the reaction mechanism, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the system (Scheme 1). The reaction was completely suppressed. The result supported a radical pathway.



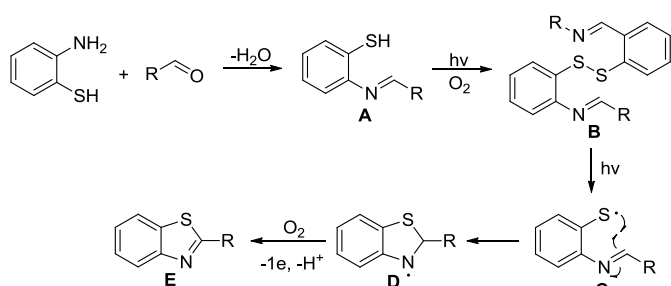
**Scheme 1.** Radical trapping experiment.

To verify the effect of photoirradiation, an experiment of on/off light was carried out (Scheme 2). In the absence of photoirradiation, the reaction of **1a** and **2a** proceeded very slowly. The significant acceleration was observed under the photoirradiation.



Scheme 2. ON/OFF light experiment.

A plausible reaction mechanism was outlined in Scheme 3. Initially, 2-iminothiophenol **A** is generated from 2-aminothiophenol and the aldehyde. Under photoirradiation, **A** is oxidized by oxygen to produce 2,2'-iminodisulfide **B**. 2-Iminophenylthiyl radical **C** is generated via light-promoted homolysis of **B**. The intramolecular addition affords the radical intermediate **D**, which is oxidized to give the final product **E**.



Scheme 3. Proposed reaction mechanism.

In summary, we have developed a visible-light-promoted synthesis of benzothiazoles from 2-aminothiophenols and aldehydes. Aromatic, heteroaromatic and aliphatic aldehydes are applicable in the transformation. The benzothiazole products could be prepared in good yields. A radical reaction pathway via the diaryl disulfide intermediates is proposed. The finding provides an efficient and convenient synthetic approach to benzothiazoles.

### Acknowledgments

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### 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, and copies of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra.

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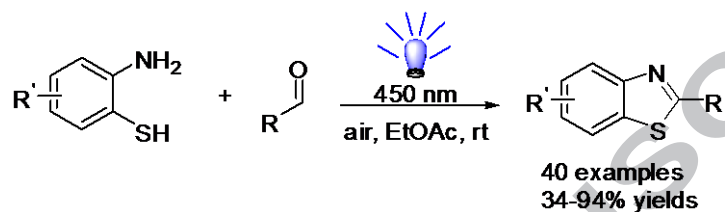
Graphical

Abstract

**Visible-light-promoted synthesis of benzothiazoles from 2-aminothiophenols and aldehydes**

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## Highlights

- An efficient and convenient synthesis of benzothiazoles from 2-aminothiophenols and aldehydes via visible-light irradiation.
- Aromatic, heteroaromatic and aliphatic aldehydes are applicable.
- A radical reaction pathway via the diaryl disulfide intermediates is proposed.

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