SYNTHESES OF 2-ARYL BENZOTHIAZOLES VIA PHOTOCATALYZED OXIDATIVE CONденSATION OF AMINES WITH 2-AMINOTHIOPHENOL IN THE PRESENCE OF BODIPY DERIVATIVES

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GRAPHICAL ABSTRACT

Abstract A simple, convenient, and efficient new method for synthesis of 2-aryl benzothiazoles under mild conditions with nonmetal catalyst has been developed. Boron–dipyrromethene (BODIPY) dyes were used as photocatalysts for aerobic oxidative reactions of amine with 2-aminothiophenol. The approach will be very useful for the synthesis of benzothiazole derivatives and the development of photocatalytic reactions.

Keywords Benzothiazoles; BODIPY; oxidation; photocatalysis; synthesis

INTRODUCTION

2-Aryl benzothiazoles play a very important role as organic functional materials in chemistry and are also widely used as biologically active products,[1,2] as well as marketed drugs or drug candidates.[3] For example, 2-aryl benzothiazoles are not only important fluorescent dyes that are used in fiber and plastic[4] but also are used as liquid crystals and off-color material.[5,6] In medicine, 2-aryl benzothiazoles serve as fungicides,[7] acaricides[8] and anticancer agents.[9]

Some synthesis methods for 2-aryl benzothiazoles have been reported in the literature.[10–17] Classic methods for the synthesis involve the condensation of 2-aminothiophenols with aryl aldehydes,[10] acyl chlorides,[11] carboxylic acids,[12]...
alcohols,[13] and amines[14] in the presence of oxidants. Another method is intramolecular cyclization reaction of \(N\)-(2-bromophenyl)benzothioamide with the Pd complex as catalyst. Moreover, it also has been demonstrated that 2-aryl benzothiazoles can be synthesized efficiently via transition-metal-catalyzed (Ni, Pd) cross-couplings between benzothiazoles and aryl halides,[15] aryl boronic acids,[16] or aromatic carboxylic acids.[17] Unfortunately, so many disadvantages, such as rigorous conditions (i.e., high temperature, long reaction time, and high pressure), hazardous oxidants,[18] or potential toxicity and high cost of the metal catalysts, presented in these synthetic reactions, result in transformations that are uneconomical and unfriendly to the environment. Therefore, a new method for its construction is highly desirable.

With the demand for green chemistry, visible-light-responsive photoredox reactions show much prominence for the use of the visible light, which is a clean energy source provided by the solar irradiance. Boron–dipyrromethene (BODIPY) is a class of novel fluorescent dyes. It is composed of dipyrromethene complexes with a substituted boron atom, typically a BF₂ unit.[19,20] Currently, BODIPY has been used as visible-light-responsive photocatalyst applied in oxidation of thioanisole and dihydroxynaphthalenes,[21,22] which shows excellent photocatalytic activity. In these reactions, oxygen/air was used as the terminal oxidant. Mild conditions and metal-free photoredox reaction driven by the BODIPY photosensitizer make it highly economical for their excellent properties such as strong fluorescence and absorption. Meanwhile, the molecular structure of BODIPY can be so easily tuned by a way of small modifications that we can choose a better catalyst to photocatalyze the oxidative reaction. In this context, one-pot synthesis of 2-aryl benzothiazoles via BODIPY-photocatalyzed oxidation of amines with 2-aminothiophenol in visible light was explored.

**RESULTS AND DISCUSSION**

There are several BODIPY photocatalysts discussed in this article. As shown in Scheme 1, BODIPY 1 is made from aldehyde as electrophilic component to form the methane bridge between two pyrrole units. Then BODIPY 2 and BODIPY 3 are synthesized by using copper(II) bromide as bromination reagents in mild conditions.

![Scheme 1. Synthesis of BODIPYs.](image-url)
with excellent yields and selectivity. Their structures are confirmed by the $^1$H NMR, $^{13}$C NMR, and mass (MS) spectra. With BODIPYs in hand, we further studied the photophysical properties of these compounds. BODIPYs are colorful to our eyes, and most of them are brilliant upon irradiation. UV-vis absorption and fluorescence spectra of BODIPYs were studied (see Fig. 1).

BODIPYs’ spectra show the typical narrow absorption and sharp fluorescence emission bands of classic difluoroboron dipyrrins, and the maximum fluorescence emission band (BODIPY 3b, the blue dashed line in Fig. 1) can approach 580 nm, which displays near-IR emission. With the increased conjugation on BODIPY b molecule, the spectra are red-shifted (10 nm for absorption and 10 nm for fluorescence emission) compared with those of BODIPY a. Meanwhile, with the increase of the amount of bromine atom in the BODIPY structure, obvious red shifts of the absorption and emission was observed in BODIPY 3a, and the Stokes shift are 10 nm and 20 nm respectively compared with BODIPY 1a and BODIPY 2a. On the other hand, fluorescence quantum yield was weakened to a great extent for this reason (see Table 1).

Figure 1. Steady-state UV–vis absorption (solid line) and fluorescence (dashed line) spectra measured in dichloromethane.
To solve the problems that occur in synthesis of 2-aryl benzothiazoles mentioned previously, one-pot synthesis of 2-aryl benzothiazoles via BODIPY-photocatalyzed oxidation of amines with 2-aminothiophenol in visible light was explored. We are aimed at accomplishing the transformation effectively under a mild condition with nonmetal catalyst.

Results of control experiments and optimization of reaction conditions for the oxidation of benzylamine are shown in Table 2. Initially, the reaction was conducted without visible light (Table 2, entry 6), and no product was detected in gas chromatography (GC). Similarly, no transformation occurred in the absence of oxygen even with longer reaction time to 8 h (Table 2, entry 5). When the reaction was conducted under light without BODIPY catalyst, no product was observed either (Table 2, entry 7). Meanwhile, we also found the mounts of 2-aminothiophenol (from 2 to 3 eq) and

| Entry | Photosensitizer | Condition | Temp. (°C) | Time (h) | Yield (%) |
|-------|-----------------|-----------|------------|----------|-----------|
| 1     | BODIPY 1a/1b    | In air    | 23         | 5        | 24/22     |
| 2     | BODIPY 2a/2b    | In air    | 23         | 5        | 31/28     |
| 3     | BODIPY 3a/3b    | In air    | 23         | 5        | 40/36     |
| 4     | BODIPY 3a       | In air    | 50         | 5        | 80        |
| 5     | BODIPY 3a       | In N₂     | 50         | 10       | —         |
| 6°    | BODIPY 3a       | In air    | 50         | 5        | —         |
| 7     | No catalyst     | In air    | 50         | 5        | —         |
| 8°    | BODIPY 3a       | In air    | 50         | 5        | —         |
| 9     | BODIPY 3a       | In O₂     | 50         | 5        | 83        |
| 10    | BODIPY 3a       | In air    | 80         | 5        | 73        |

°Reaction conditions: benzylamine (1 mmol), 2-aminothiophenol (2 eq, 2 mmol), photosensitizer catalyst (1 mol%), acetonitrile as solvent (5 mL), λ > 380 nm, P = 0.20 MPa.

°°Yield are determined by GC.

°°°No photoirradiation.

°°°°2-Aminothiophenol (3 eq, 3 mmol).

°°°°°No reaction.
the reaction atmosphere (air to O₂) just have a slight effect on the reaction results, for
the yields only rise 2% and 3% respectively. Therefore, the conclusion was made as
follows: the light, photosensitizer, and oxygen are essential to the photocatalytic
oxidation. Subsequently, a better yield (80%) was obtained with temperature rising
to 50°C (Table 2, entry 4). We further raised the reaction temperature to 80°C
(Table 2, entry 10), and GC shows that more side products were generated (the main
side product is benzaldehyde). By changing the photosensitizer, however, compared
with BODIPY 1 and BODIPY 2, it is obvious that BODIPY 3 presents significant
influences in the aerobic oxidation of benzylamine with 2-aminophenol at the
same condition (Table 2, entries 1–3). As the amount of bromine in the BODIPY
structure increases, better yields are obtained, which may suggest that bromine can
promote the generation of ¹O₂ in accordance with some reported results that the
bromine-substituted BODIPY strongly promoted the generation of ¹O₂.[23,24] Based
on these results, we decided to set heating the benzylamine and 2-aminophenol
at 50°C in the presence of BODIPY 3a irradiated by a 35-W xenon lamp as our
optimized condition.

With the optimized protocol results in hand, a number of experiments were car-
ried out to explore the scope and limitation of the reaction (Table 3). We found that
the reaction worked very well for a wide variety of substituted benzylamines, obtain-
ing the expected substituted benzothiazoles in yields ranging from 42 to 81%. With
various substituents such as methyl, chloro, fluoro, bromine, and methoxy as well
as naphthyl, all groups proceeded smoothly in good yields. For example, benzyla-
mines substituted with electron-donating groups (CH₃ and OCH₃) (Table 3, entries
3, 4, and 11) afford the target products in 78–81% yields. Halogens such as chloro
and bromine (Table 3, entries 6, 9, and 10) give no problems for para-substituted ben-
zylamines, meta or ortho, except the fluoro (Table 3, entries 2 and 7), which are strong
electron-withdrawing groups and only undergo the oxidative condensation with 42%
yields. So the oxidation of the electron-donating groups proceeded more efficiently
than the electron-withdrawing groups. We also found that no reaction occurred when
amine lacked α-H, such as aniline (Table 3, entry 15). Heterocyclic amine, such as
thiophen-2-ylmethanamine, also proceeded smoothly with better yield.

Based on these foregoing results, we proposed a mechanism that it is highly
likely that the presence of singlet oxygen (¹O₂)[25] is responsible for the photooxida-
tion of benzylamine with 2-aminophenol. We further studied the influence of
DABCO (1,4-diazabicyclo[2.2.2]octane, a singlet oxygen scavenger) to the oxi-
dation. We found that the photocatalytic reaction can be significantly quenched
by the DABCO (Table 4). Therefore, we think ¹O₂ is involved in the photooxido-
ative process. The proposed mechanism is shown in Scheme 2. First, BODIPY accepted
a photon from the visible light to form BODIPY* under the irradiation by visible light.
Then, benzylamine was oxidized to form phenylmethanimine by singlet oxygen gen-
erated by energy transfer from BODIPY*. Finally, 2-aryl benzothiazole was formed
by the condensation of intermediate. Some details about the singlet oxygen involved
in the photosensitized oxidation reaction had been reported and discussed.[26,27] In
terms of the energy requirements, BODIPY dyes generating singlet oxygen from the
triplet excited state have been used in photodynamic therapy.[28–30]

In summary, several BODIPY dyes were synthesized, and their structures
were confirmed by ¹H NMR, ¹³C NMR, and MS spectra, and they were used as
Table 3. Oxidation of various substituted amines using BODIPY 3a<sup>a</sup>

| Entry | Substrate | Product | Time (h) | Yield (%)<sup>b</sup> |
|-------|-----------|---------|---------|------------------------|
| 1     | \( \text{NH}_2 \) | ![Product 1](image) | 5       | 80                     |
| 2     | \( \text{NH}_2 \) | ![Product 2](image) | 5       | 42                     |
| 3     | \( \text{NH}_2 \) | ![Product 3](image) | 5       | 81                     |
| 4     | \( \text{NH}_2 \) | ![Product 4](image) | 5       | 78                     |
| 5     | \( \text{NH}_2 \) | ![Product 5](image) | 5       | 76                     |
| 6     | \( \text{NH}_2 \) | ![Product 6](image) | 5       | 72                     |
| 7     | \( \text{NH}_2 \) | ![Product 7](image) | 5       | 49                     |
| 8     | \( \text{NH}_2 \) | ![Product 8](image) | 5       | 69                     |
| 9     | \( \text{NH}_2 \) | ![Product 9](image) | 5       | 75                     |
| 10    | \( \text{NH}_2 \) | ![Product 10](image) | 5       | 74                     |

(Continued)
photocatalysts for aerobic oxidative reactions of amine with 2-aminothiophenol. A new method to synthesize 2-aryl benzothiazoles under a mild condition with a metal-free procedure using BODIPY as photocatalysts was developed. Our

| Entry | Substrate | Product | Time (h) | Yield (%)\(^b\) |
|-------|-----------|---------|----------|-----------------|
| 11    |           |         | 5        | 79              |
| 12    |           |         | 5        | 78              |
| 13    |           |         | 5        | 76              |
| 14    |           |         | 5        | 81              |
| 15    |           |         | 5        | 0               |

\(^a\)Reaction conditions: amine (1 mmol), 2-aminothiophenol (2 eq., 2 mmol), BODIPY 3a (1 mol%), acetonitrile as solvent (5 mL), \(\lambda > 380\,\text{nm}\), \(T = 50\,^\circ\text{C}\), in air \(P = 0.20\,\text{MPa}\).

\(^b\)Isolated yield based on amine.

**Table 4.** Mechanism study of the oxidative experiments\(^a\)

| Entry | Add DABCO (%) | Yield (%)\(^b\) |
|-------|---------------|-----------------|
| 1     | 0             | 80              |
| 2     | 2             | 35              |
| 3     | 5             | 0               |

\(^a\)Reaction conditions: benzylamine (1 mmol), 2-aminophenol (2 mmol), photosensitizers catalyst (1 mol%), acetonitrile (5 mL), in air \(P = 0.2\,\text{MPa}\), \(\lambda > 380\,\text{nm}\), 50\,\text{°C}.

\(^b\)Yield was determined with GC.
approach will be very useful for the synthesis of benzothiazoles derivatives and the development of photocatalytic reactions.

EXPERIMENTAL

**General Procedure for BODIPY 1**

Aryl-aldehyde (2.0 mmol) and 2,4-dimethylpyrrole (423 mg, 4.5 mmol) were dissolved in (100 mL) absolute CH₂Cl₂. Trifluoroacetic acid (one drop) was added in the solution under argon. After the reaction mixture was stirred about 4 h at room temperature until thin-layer chromatography (TLC) showed the complete consumption of the aldehyde. Then DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (454 mg, 2.0 mmol) in CH₂Cl₂ (50 mL) was added. The mixture was stirred for 30 min followed by the addition of Et₃N (6 mL) and BF₃·Et₂O (4 mL) at ice-cold condition and further stirred at room temperature for 3 h. The reaction mixture was washed with water (3 × 100 mL), and then the organic layers were combined, dried with anhydrous MgSO₄, and evaporated to dryness. The crude product was further purified using column chromatography.

**General Procedure for BODIPY 2**

1,3,5,7-Tetramethyl-BODIPY 1 (0.2 mmol) and K₂CO₃ (0.6 mmol) were dissolved in MeCN (20 mL). CuBr₂ (0.3 mmol) in MeCN (25 mL) was slowly added in the solution under an O₂ atmosphere (balloon). The mixture was stirred at rt for 24 h. The reaction mixture was washed with EtOAc (3 × 40 mL) and then washed with H₂O (3 × 30 mL). The organic layer were combined and dried over with anhydrous MgSO₄ and evaporated to dryness. The crude product was further purified using column chromatography.

**General Procedure for BODIPY 3**

1,3,5,7-Tetramethyl-BODIPY 1 (0.2 mmol) and CuBr₂ (0.5 mmol) were dissolved in MeCN (20 mL) under an O₂ atmosphere (balloon). The mixture was stirred at rt for 12 h. The reaction mixture was washed with EtOAc (3 × 40 mL) and then washed with H₂O (3 × 30 mL). The organic layer were combined, dried over with
anhydrous MgSO₄, and evaporated to dryness. The crude product was further purified using column chromatography.

**Typical Procedures for Photocatalytic Oxidation of Amine with 2-Aminothiophenol**

Amine (1 mmol), 2-aminothiophenol (2 mmol), BODIPY photosensitizer (0.01 mmol, 1.0 mol%), and acetonitrile (5 mL) were added to a dry 10-mL flask. The flask was pressurized with air (2 bar) and then heated to 50°C. The solution was then irradiated using a 35-W xenon lamp through a cutoff filter (0.72 M NaNO₂ aqueous solution, which is transparent for light >385 nm, because lamps could emit a small amount of ultraviolet light). After the reaction was completed, the solvent was evaporated under reduced pressure. The crude product was further purified using column chromatography.

**SUPPORTING INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

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