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Le Anh Nguyen, Thai Duy Dang, Quoc Anh Ngo, T .B. Nguyen. Sulfur-Promoted Synthesis of Benzoxazoles from 2-Aminophenols and Aldehydes. *European Journal of Organic Chemistry*, 2020, 2020 (25), pp.3818-3821. 10.1002/ejoc.202000523 . hal-02993895

**HAL Id: hal-02993895**

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Submitted on 24 Nov 2020

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# Sulfur-promoted Synthesis of Benzoxazoles from 2-Aminophenols and Aldehydes

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**Abstract:** Elemental sulfur ( $S_8$ ) was found to be an excellent stoichiometric oxidant to promote oxidative condensation of 2-aminophenols with a wide range of aldehydes, including aliphatic aldehyde such as cyclohexanecarboxaldehyde. The reactions were catalyzed by sodium sulfide in the presence of DMSO as additive. The benzoxazole products were obtained in satisfactory yields. The reaction conditions could be applied to larger syntheses (10-50 mmol).

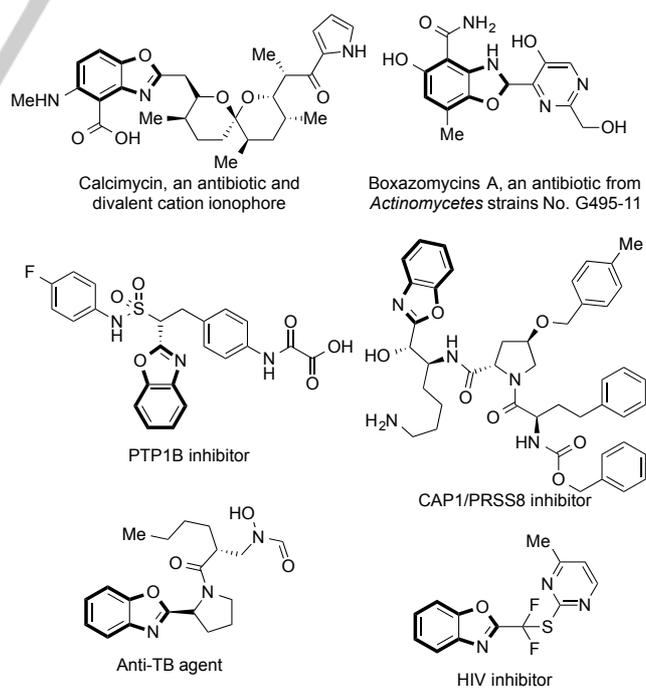
Benzoxazole derivatives have attracted considerable attention due to the presence of this heterocyclic motif in a variety of natural products and bioactive molecules (Figure 1).<sup>[1],[2]</sup>

The most commonly used synthetic approach to such molecules involve condensation of 2-aminophenols with carboxylic acids<sup>[3],[4]</sup> or derivatives<sup>[5],[6]</sup> under non oxidant conditions or with alcohols,<sup>[7],[8]</sup> amines,<sup>[9],[10]</sup> ketones,<sup>[11]</sup> aldehydes,<sup>[12]-[15]</sup> methylarenes<sup>[16]</sup> or related compounds<sup>[17]</sup> in the presence of an oxidant or at high temperatures with concomitant dehydrogenation.<sup>[18]-[19]</sup> However, most of the traditional synthetic methods required strongly acidic conditions<sup>[6]</sup>, prolonged heating at high temperatures and significant amounts of catalysts<sup>[14]</sup> (including expensive/toxic transition metal catalysts)<sup>[5],[7],[13],[15]-[16],[18]-[21]</sup> as well as toxic/harmful reagents and solvents.<sup>[3],[4],[8],[12],[16]</sup>

Although the aerobic oxidation<sup>[12],[15],[20]-[21]</sup> is in general very green because of its high atom economy with water as the only stoichiometric byproduct in most cases, a major drawback of using oxygen as an oxidant is the risk of explosion of flammable organic substrates, especially in large-scale syntheses at reaction temperatures above the flashpoint of the reaction components. Moreover, due to its gaseous state, exact stoichiometric control of oxygen amounts used in the reaction is not readily possible. The reaction requires high volume of gas if performed at 1 atm without bubbling the gas through the reaction mixture. As a matter of fact, 11.2 L of oxygen under standard conditions for temperature and pressure has the same equivalent as 32 g or 16 mL of solid  $S_8$ . Consequently, over oxidation as well as oxidation reactions of other functional groups present in the molecules are among the most encountered side reaction of aerobic oxidation, especially for high-pressure reactions at high temperature.

In this context, using other alternative oxidants that could avoid the above-mentioned drawbacks of oxygen to perform selectively and cleanly the oxidation transformation would be highly desirable, especially for large-scale productions.

Recently, our laboratories are interested in using elemental sulfur as a versatile tool in organic synthesis of a wide range of molecules of interest.<sup>[22]-[27]</sup> As a waste of oil and gas industry with annual global production around 70 million metric tons, sulfur is an inexpensive and user-friendly starting material due to its physical properties as well as its low reactivity under ambient conditions. Interestingly, under suitable thermal or catalytic activation, sulfur displays a wide range of reactivities that can be useful in the development of new redox transformation.



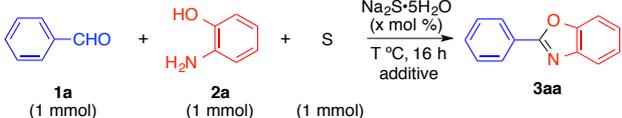
**Figure 1.** Natural products and bioactive molecules containing benzoxazole core

## COMMUNICATION

In continuation of our interest in the exploration of new and useful chemical behavior of elemental sulfur, we report herein the use of this element as a stoichiometric oxidant to promote oxidative coupling of 2-aminophenols with aldehydes to provide 2-substituted benzoxazoles.

Initially, the reaction between equimolar amount of benzaldehyde **1a**, 2-aminophenol **2a** and elemental sulfur was selected as a model reaction for optimization as summarized in Table 1. Inexpensive hydrated sodium sulfide  $\text{Na}_2\text{S}\cdot 5\text{H}_2\text{O}$  was chosen as a catalyst to activate elemental sulfur.<sup>[28]</sup>

**Table 1.** Screening of the reaction conditions



Entry <sup>[a]</sup>	Additive	x (mol %)	T (°C)	Yield (%)
1	-	10	80	ND <sup>[b]</sup>
2	DMSO (0.1 mL)	10	80	69
3	<b>DMSO (0.1 mL)</b>	<b>10</b>	<b>70</b>	<b>72</b>
4	DMSO (0.1 mL)	10	90	67
5	DMSO (0.1 mL)	10	60	ND <sup>[b]</sup>
6	DMSO (0.2 mL)	0	70	62
7	DMSO (0.05 mL)	0	70	65
8	DMF (0.1 mL)	10	70	0
9	DMAc (0.1 mL)	10	70	0
10 <sup>[c]</sup>	DMSO (0.1 mL)	10	70	0
11 <sup>[d]</sup>	DMSO (0.1 mL)	10	70	71

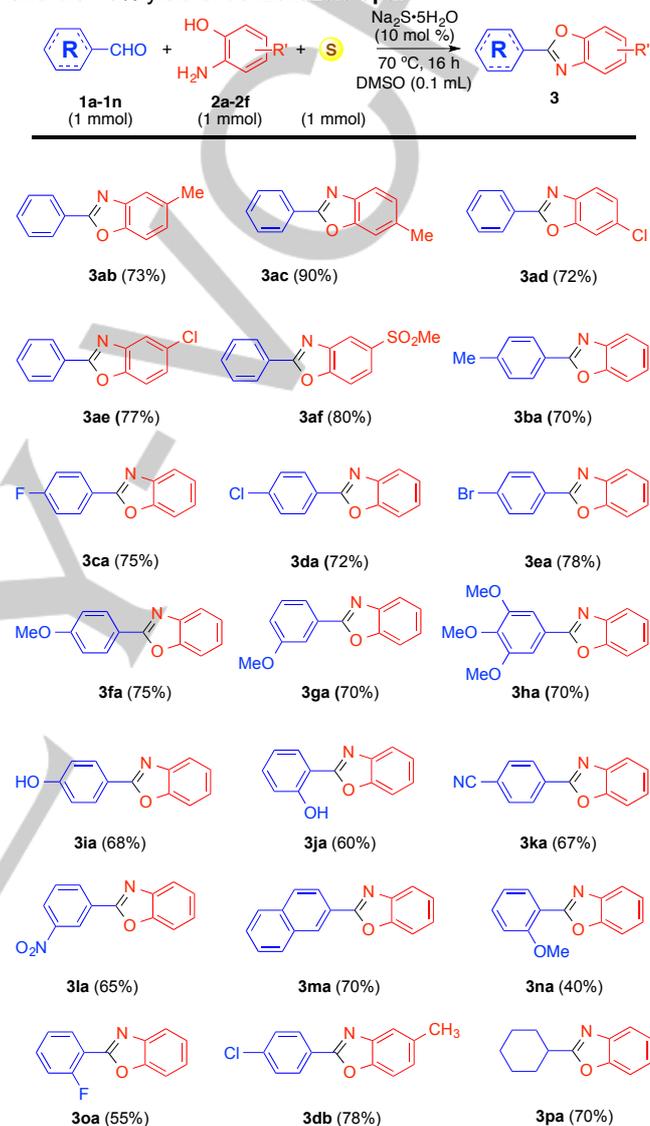
<sup>[a]</sup> Reaction performed under an argon atmosphere. <sup>[b]</sup> Not determined. <sup>[c]</sup> Reaction without elemental sulfur. <sup>[d]</sup> Reaction performed under air (1 atm).

The model experiment conducted at 80 °C in the absence of any additive did not lead to the expected product **3aa** (entry 1). Gratifyingly, in the presence of DMSO (0.1 mL, 1.5 equiv), the starting materials were completely consumed, the desired product **3aa** was isolated in 69% (entry 2). Further screening of other temperatures (entries 3-4) revealed that the reaction was best performed at 70 °C (entry 3). While variation of DMSO quantities did not lead to any improvement (entries 6-7), the important role of DMSO was clearly demonstrated as other aprotic additives such as DMF or *N,N*-dimethylacetamide (DMAc) (entries 8-9) failed to promote the oxidative coupling. The role of sulfur as oxidant was confirmed as its absence in the reaction mixture did not lead to the benzothiazole product (entry 10).

Finally, in view of the high yield, the best reaction conditions were selected as indicated in entry 3. For comparison purpose, the optimal reaction repeated under air atmosphere led to similar yield. With the optimized conditions in hand, we evaluated the synthetic potential of this reaction with various 2-aminophenols and a range of aromatic aldehydes (Scheme 1). In general, most of reactions proceeded smoothly to give the expected 2-substituted benzoxazoles in good to excellent yields regardless of the electronic character of substituents on the aromatic moieties of

both starting materials. 2-Aminophenols bearing alkyl, chloro as well as methylsulfone groups are competent substrates to provide benzoxazole **3ab-3af**. In a similar manner, methyl, halogen and methoxy groups as well as hydroxy, cyano or nitro groups in benzaldehyde substrates were found to be compatible with the present reaction conditions.

More importantly, the reaction conditions could also be applied to an aliphatic aldehyde such as cyclohexanecarboxaldehyde to afford a 70% yield of benzoxazole **3pa**.

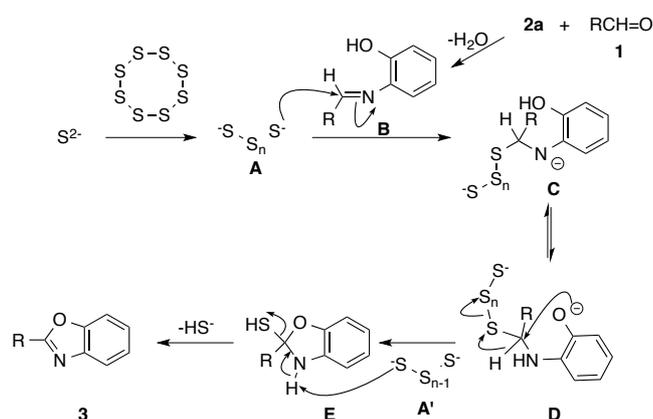


**Scheme 1.** Scope of 2-aminophenols **1** and aldehydes **2**

Finally, the synthesis of 2-phenylbenzoxazole **3aa** from 2-aminophenol and benzaldehyde was performed in larger scales (10 mmol and 50 mmol). In both case, the expected 2-phenylbenzoxazole product was obtained in comparable yields (70 and 68%, respectively) after a simple aqueous workup, extraction with dichloromethane and filtration through a short pad of silica gel.

On the basis of these results and our previous works, a reasonable mechanism is proposed as depicted in Scheme 2. With the assistance of sulfide anion from sodium sulfide as a

Lewis base catalyst for ring opening of elemental sulfur, highly nucleophilic polysulfide anions **A** were formed and engage in the addition to imine **B** generated from condensation of aldehyde **1** with 2-aminophenol **2a**. The resulting polysulfide-amide **C** could undergo a proton shift to provide phenolate **D**, which could cyclize to benzoxazoline **E**. The aromatization **E** to the final product **3** serves as a driving force to trigger the elimination of a hydrogen sulfide assisted by the resultant polysulfide **A'**. It is possible the role of DMSO is to stabilize key anionic intermediates **B-C**.



Scheme 2. Proposed reaction mechanism

Although hydrogen sulfide  $\text{H}_2\text{S}$  is a primary byproduct of the reaction, this toxic gas is trapped in the reaction medium. Indeed, we did not observe any overpressure throughout the reaction. While the exact mechanism of this process is not fully understood, we suggest that  $\text{H}_2\text{S}$  reacts with DMSO to regenerate sulfur and release dimethyl sulfide.<sup>[29]</sup> This volatile liquid (bp 37.3 °C) is in turn kept in the reaction medium by complexing with DMSO. In fact, we observe the presence of dimethyl sulfide by  $^1\text{H}$  NMR even the reaction temperatures were 70–80 °C.

In conclusion, we have developed an efficient method for the synthesis of 2-substituted benzoxazoles from 2-aminophenols and aldehydes by using in expensive elemental sulfur in stoichiometric amount as an oxidant and  $\text{Na}_2\text{S}\cdot 5\text{H}_2\text{O}$  as sulfur activating catalyst in minimum amount of DMSO. Compared to similar reactions using oxygen as oxidant, our method is characterized by its simplicity with low reaction volume while avoiding high pressure apparatus even for larger scales (10–50 mmol).

## Acknowledgements

We thank Vietnam Academy of Science and Technology for valuable financial support (KHCBHH.01/18-20).

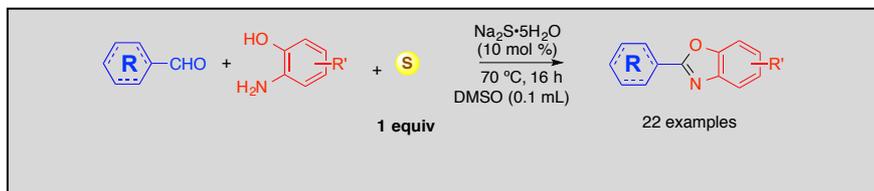
**Keywords:** elemental sulfur • oxidative coupling • aldehyde • 2-aminophenol • benzoxazole

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Oxidation with sulfur: Elemental sulfur ( $\text{S}_8$ ) was found to be an excellent stoichiometric oxidant to promote oxidative condensation of 2-aminophenols with a wide range of aldehydes to provide benzoxazoles.

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