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Peroxide-mediated oxidative coupling of primary alcohols and disulfides: synthesis of 2-substituted benzothiazoles

Nathalia B. Padilha,[a] Filipe Penteado,[a] Maria C. Salomão,[a] Eric F. Lopes,[a] Luana Bettanin,[a] Daniela Hartwig,[a] Raquel G. Jacob[a] and Eder J. Lenardão[a,*]

[a]*Laboratório de Síntese Orgânica Limpa - LASOL - CCQFA - Universidade Federal de Pelotas - UFPel - P.O. Box 354 - 96010-900, Pelotas, RS, Brazil.*

** e-mail: lenardao@ufpel.edu.br; phone/FAX: +55 53 3275 7533.*

ABSTRACT

A peroxide-mediated protocol for the synthesis of 2-substituted benzothiazoles was developed, starting from bis(*o*-aminophenyl) disulfides and primary alcohols. Eleven differently 2-substituted benzothiazoles were prepared in moderate to excellent yields using di-*tert*-butylperoxide (DTBP) as an oxidant.

Keywords: benzothiazoles; C-S bond formation; oxidative coupling; disulfides

INTRODUCTION

Nitrogen-containing heterocycles are one of the most important classes of naturally occurring compounds, with a crucial role in many biological processes. They represent the active pharmaceutical ingredient of countless drugs, are present in high-performance materials and are used as dyes.[1] Among this impressive class of compounds, 2-substituted benzothiazoles have attracted significant attention, since this subclass is present in the core motif of various bioactive compounds, playing a crucial role in drug discovery.[2] In this context, the most famous 2-substituted benzothiazole derivative is Riluzole® (**1**), a worldwide marketed drug, used for the treatment of amyotrophic lateral sclerosis (ALS), a motor neuron disease.[3] In addition to the importance of these compounds as therapeutics, they also have attracted attention due to their photophysical properties.[4] For instance, thioflavin T (**2**) has been extensively used for the detection of deposited amyloid fibrils in humans, which are related to the development of several diseases, including Alzheimer's (AD) and Parkinson's diseases (PD).[5] In this context, Pittsburgh Compound B (**3**), a radiative analogue of thioflavin T, was clinically approved for AD diagnosis, through amyloid-imaging positron emission tomography (PET) (Scheme 1).[6]

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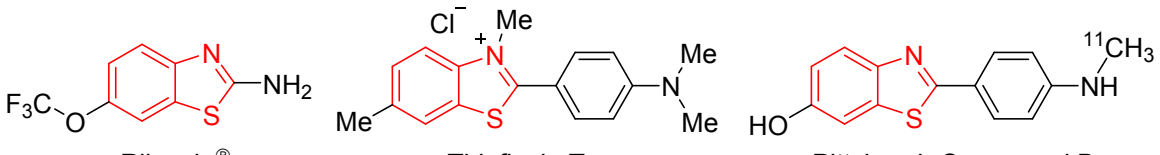

Riluzole® **1** | Thioflavin T **2** | Pittsburgh Compound B **3**

Scheme 1. Representative important 2-substituted benzothiazoles.

As a consequence of the notable biological properties of 2-substituted benzothiazoles, the development of efficient synthetic methodologies to access these compounds selectively is highly desirable.[7] The most widespread strategy to construct 2-substituted benzothiazoles is *via* the condensation reaction between 2-aminobenzenethiol or 2-aminoaryldisulfides and carbonyl partners, including aldehydes[8] and organic acid derivatives, such as, carboxylic acids,[9] amides,[10] acyl chlorides[11] and α-keto acids.[12] Additionally, C-H activation strategies using 2*H*-benzothiazoles as starting materials, have been investigated.[13] In this context, alcohols have been explored as substrates in dehydrogenative annulation reactions with 2-aminobenzenethiol *via* transition metal-catalyzed,[14] strong base-catalyzed[15] and electrochemical-assisted[16] synthetic strategies. These protocols however, present some drawbacks, including long reaction times and complex reaction apparatus. Thus, the development of methods using simple, ease to handle and widely available substrates for the synthesis of 2-substituted benzothiazoles is desirable. Herein, we describe a simple and efficient peroxide-mediated dehydrogenative annulation of alcohols and 2-aminoaryldisulfides to access 2-alkyl and 2-aryl benzothiazole derivatives.

RESULTS AND DISCUSSION

Initially, bis(*o*-aminophenyl) disulfide **4a** (prepared *via* the mild DMSO-promoted oxidation of 2-aminobenzenethiol)[17] and ethanol **5a** were examined as model substrates using di-*tert*-butyl peroxide (DTBP; 2 equiv.) as the oxidant, aiming to prepare 2-methylbenzo[*d*]thiazole **6a** (Table 1). The first reactions were performed at 120 ºC in a sealed tube, and after stirring for 3 h and 6 h, the desired product **6a** was formed in 17% and 25% yield, respectively (Table 1, entries 1-2). In order to investigate the influence of the temperature in this transformation, the reaction was carried out at 150 ºC, and a remarkable improvement was observed, giving product **6a** in 61% yield after 6 h (Table 1,

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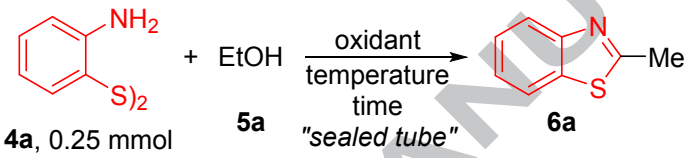
entry 3). Additionally, by increasing the amount of the oxidant to 3 and 4 equiv., a proportional increase in the yield was observed, giving product **6a** in 83% and 97% yield, respectively (Table 1, entries 4-5). Next, we evaluated the efficiency of different oxidants, including *tert*-butyl hydroperoxide (TBHP in H_2O and in decane) and H_2O_2. However, none of them were effective in the reaction, giving product **6a** in low yield (TBHP) or even failing completely (H_2O_2) (Table 1, entries 6-8). Finally, the amount of EtOH was reduced to 0.5 mL and 0.25 mL, giving product **6a** in 43% and 31% yield, respectively (Table 1, entries 9-10).

Table 1. Reaction optimization for the synthesis of **6a**.[a]



4a, 0.25 mmol **5a** **6a**

Entry	**5a** (mL)	Oxidant (equiv)	Temperature (ºC)	Time (h)	Yield **6a** (%)[b]
1	1	DTBP (2)	120	3	17
2	1	DTBP (2)	120	6	25
3	1	DTBP (2)	150	6	61
4	1	DTBP (3)	150	6	83
5	1	DTBP (4)	150	6	97
6	1	TBHP 70% in H_2O (4)	150	6	13
7	1	TBHP in decane (4)	150	6	28
8	1	H_2O_2 (4)	150	6	NR
9	0.5	DTBP (4)	150	6	43
10	0.25	DTBP (4)	150	6	31

[a] In a reaction vial were added **4a** (0.25 mmol), EtOH **5a** and the oxidant. The reaction vial was sealed, and the mixture stirred for the stated temperature and time. [b] Reaction yields were obtained after preparative thin-layer chromatography.

With the optimized reaction conditions in hand (Table 1, entry 5),[18] the scope and limitations for the reaction of bis(*o*-aminophenyl) disulfide **4a** with several primary alcohols **5** was performed (Table 2). *n*-Butanol **5b** ($R^1 = C_3H_7$) and isoamyl alcohol **5c** ($R^1 = C_5H_{11}$) were suitable substrates, giving the respective products **6b** and **6c** in 55% and 40% yield, respectively. These are interesting results, because the synthesis of 2-alkyl-substituted benzothiazoles is not trivial, with a reduced number of methods compared to their 2-aryl

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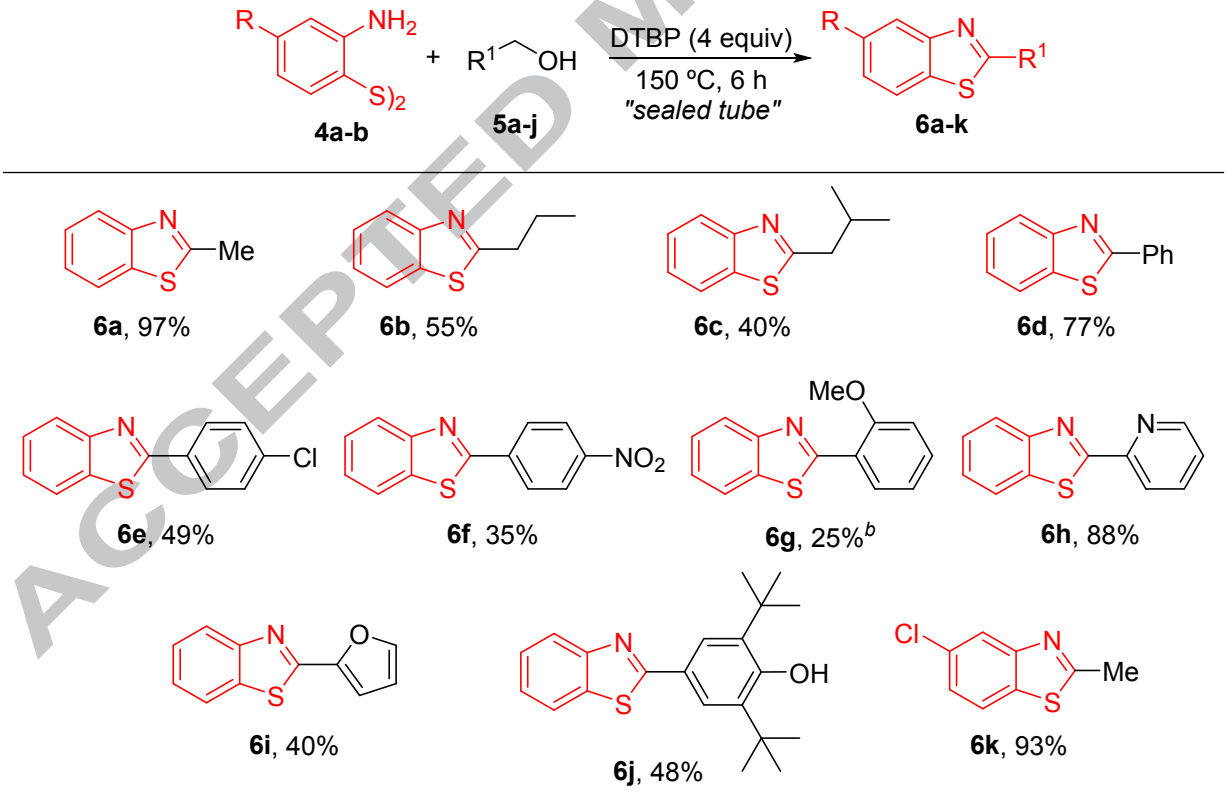
analogues.[7] Benzyl alcohol **6d** and its derivatives were also tolerated in the reaction, affording the respective 2-arylbenzothiazoles in modest to good yields. Thus, product **6d** (R^1 = C_6H_5) was obtained in 77% yield, while the *para*-substituted **6e** (R^1 = 4-ClC_6H_4) and **6f** (R^1 = 4-$NO_2C_6H_4$) were isolated in 49% and 35% yield respectively, after 6 h. A longer reaction time of 10 h was necessary when sterically hindered *ortho*-substituted benzylic alcohol **5g** (R^1 = 2-$MeOC_6H_4$) was used, giving the expected product **6g** in 25% yield. Additionally, 2-pyridylbenzothiazole **6h** was formed in 88% yield, while 2-furfurylbenzothiazole **6i** was obtained in 40% yield. The bulky 2,6-di-*tert*-butyl-4-(hydroxymethyl)phenol **5j** reacted smoothly with **4a** to give the expected product **6j** in 48% yield (Table 2). The presence of an electron-withdrawing group (Cl) in the *para*-position of bis(*o*-aminophenyl) disulfide (**4b**) did not influence the reactivity with ethanol **5a**, affording the respective benzothiazole **6k** in 93% yield.

Table 2. Study of the reaction scope for the synthesis of products **6**.[a]



[a] In a reaction vial were added the substrate **4** (0.25 mmol), the alcohol source **5** (1 mL) and DTBP (4 equiv). Then, the reaction vial was sealed, and the solution stirred for 6 h at 150 °C. Reaction yields were obtained after preparative thin-layer chromatography. [b] Reaction was carried out for 10 h.

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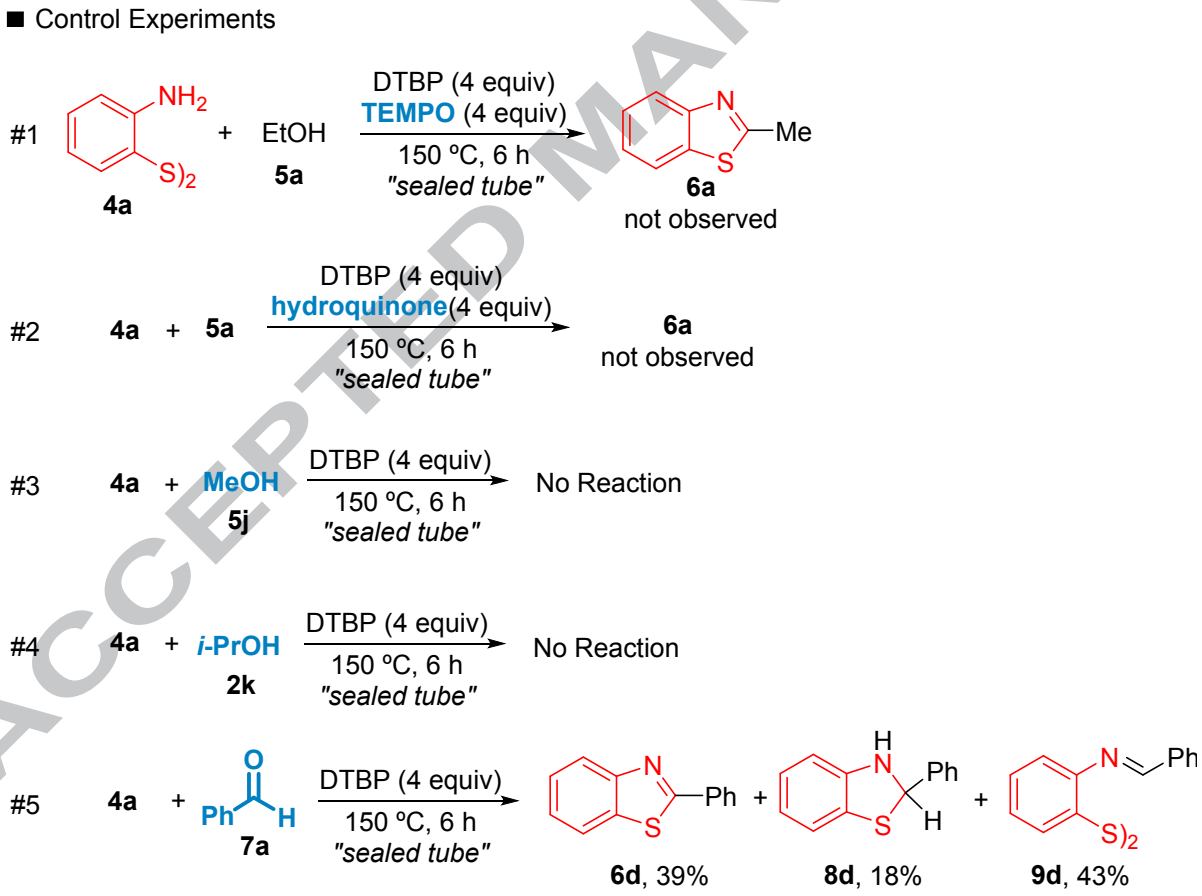
Thus, in order to gain mechanistic insights into this protocol, several control experiments were performed (Scheme 2). Initially, the reaction between **4a** and **5a** was carried out in the presence of TEMPO and hydroquinone as radical scavengers. In both cases the formation of compound **6a** was not observed, meaning that radical species are involved in key reaction steps (Scheme 2, #1 and #2). When MeOH **5j** was used as the alcohol source instead of ethanol, the respective benzothiazole was not detected, and the starting disulfide **4a** was recovered (Scheme 2, #3). The same result was obtained when *i*-PrOH **5k** (a secondary alcohol) was employed in the reaction with **4a** (Scheme 2, #4). Finally, benzaldehyde **7a** was employed instead of EtOH **5a** under the standard reaction conditions, and after 6 h at 150 °C, bis(*o*-aminophenyl) disulfide **4a** was completely consumed to give the expected product **6c** in 39% yield, together the dihydro-derivative **8d** (18%) and the imine derivative **9d** (43% yield) (Scheme 2, #5).



Scheme 2. Control experiments under the optimized reaction conditions.

Taken together, these results suggest that a radical process is involved and that the stability of the radical species is important; presumably the reaction did not work with MeOH because it would generate an unstable methyl radical. Additionally, the use of

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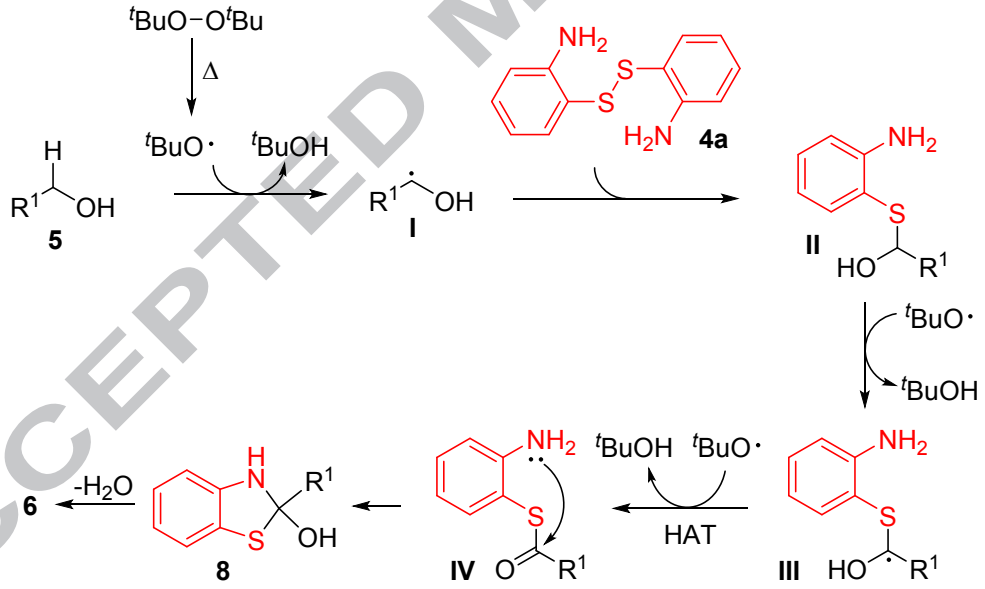
primary alcohols is mandatory to provide two hydrogen atoms for the required radical oxidation steps. It was also confirmed that the reaction proceeds *via* the oxidation of the alcohol substrate to an aldehyde; however, utilization of the alcohol is mandatory to afford the product in acceptable yields (Scheme 2).

Thus, based on the control experiments and previous reports,[19] a plausible reaction mechanism was proposed. Initially, DTBP is decomposed under heating to the radical ^{t}BuO•, which promotes a radical oxidation of the primary alcohol **5** to the radical species **I**. Subsequently, the S-S bond of substrate **4a** undergoes radical substitution by radical intermediate **I**, giving the thioether intermediate **II**. Hence, oxidation of intermediate **II** affords the radical intermediate **III**, which in the presence of the *tert*-butoxyl radical undergoes a hydrogen atom transfer (HAT) reaction to give intermediate **IV**. After the intramolecular annulation of ketone **IV**, the respective dihydrobenzothiazole **8** is formed. Finally, a dehydration reaction converts intermediate **8** into the desired product **6** (Scheme 3).



Scheme 3. Plausible reaction mechanism for the synthesis of benzothiazole **6**.

CONCLUSION

In summary, we have described a new and general protocol to prepare 2-substituted benzothiazoles in moderate to excellent yields. The good tolerance to access 2-alkyl-substituted benzothiazoles, which are in general difficult to prepare, and the use of readily available primary alcohols as starting material are notable features of the method. In

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addition, this protocol avoids the use of unpleasant smelling thiols, which are commonly used as substrates in the synthesis of 2-substituted benzothiazoles.

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18. **General procedure for the preparation of the 2-substituted benzothiazoles 6a-k:** In a 5 mL glass ampoule were added the disulfide **4a** or **4b** (0.25 mmol), the primary alcohol **5a-j** (1.0 mL for liquids and 1.0 mmol for solids) and DTBP (4 equiv). Then, the ampoule was sealed, and the system was heated (150 ºC) for 6 h under magnetic stirring. Upon reaction completion, the unreacted volatile alcohol derivatives were removed by vacuum and the desired product was isolated by preparative thin-layer chromatography using a mixture of hexanes and AcOEt. Spectroscopic data for all of the prepared compounds are available in the Supporting Information.

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