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Graphical Abstract

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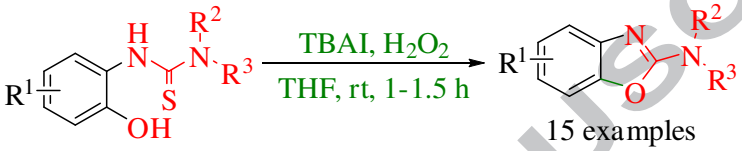

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Iodide catalyzed synthesis of 2-aminobenzoxazoles via oxidative cyclodesulfurization of phenolic thioureas with hydrogen peroxide

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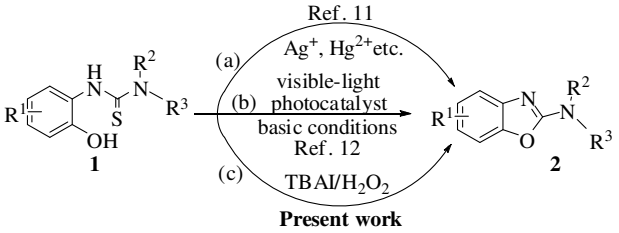
ABSTRACT

A convenient and efficient oxidative cyclodesulfurization of *o*-phenolic thioureas to 2-aminobenzoxazoles employing TBAI (tetrabutylammonium iodide)/H_2O_2 catalyst/reagent system is reported. The protocol utilizes and offers a number of desired features such as metal-free, base-free, simple operation, room temperature, low cost catalyst/reagent, no need for anhydrous and inert conditions. The approach is also applicable to a one-pot synthesis of 2-aminobenzoxazoles in an excellent yield starting directly from *o*-aminophenols and aryl isothiocyanates.

A major goal in synthetic organic chemistry is the development of a resourceful and reliable method, which would minimize the cost and chemical waste. In general, catalytic processes are much economical and produce far less waste as compared to reactions that use stoichiometric amounts of reagents. Iodide or hypervalent iodine promoted organic reactions have received considerable attention and experienced impressive advancement during the past few years.[1] In recent years, the combination of tetrabutylammonium iodide (TBAI) as a catalyst and *tert*-butyl hydroperoxide (TBHP) or hydrogen peroxide as an oxidant has emerged as an environmentally benign non-metal system with superb oxidizing power.[1a,d,2,3] Additional advantages of this oxidizing system particularly include low cost, low toxicity, mild reaction conditions, and isolation of products free from any metal contaminations. To date, many reactions have been optimized using the TBAI-TBHP or TBAI-H_2O_2 system for the formation of carbon-carbon,[4] carbon-oxygen,[3a-e,5] carbon-nitrogen,[1e,3f-j,6] and carbon-sulfur bonds.[2a,7] Recently, Ishihara and Uyanik have efficiently utilized the TBAI–H_2O_2 system for the C-O bond[3e,f] and Nachtsheim et al. reported C-N bond formation.[3j] All these bond formations are enabled by *tert*-butoxyl, *tert*-butylperoxy and hypoiodite generated from iodide catalyzed decomposition of oxidants.[3e,h,6,7]

2-Aminobenzoxazoles possess useful biological properties, and this heterocyclic unit is an important building block for a variety of pharmaceutical products.[8] Some of these promising pharmaceuticals are used for the treatment of disorders, such neurodegeneration, Alzheimer's disease, HIV, schizophrenia and inflammatory disease.[8] Owing to their chemical and biological importance, numerous strategies are available for the synthesis of 2-aminobenzoxazoles, which include: (i) direct coupling of benzoxazoles or 2-halogenated benzoxazoles with an amine or its surrogates,[3j,8a,9] (ii) ring opening of benzoxazoles with secondary amines followed by oxidative cyclization with various reagents,[10] (iii) cyclodesulfurization of *o*-phenolic thioureas using metallic reagents/catalysts such as $AgNO_3$,[11a] HgO,[11b] NiO_2,[11c] LiOH/H_2O_2,[11d] KO_2[11e] or $FeCl_3$[11f] (Scheme 1a).[11] Very recently, we have reported an efficient cyclodesulfurization of *o*-phenolic thioureas to 2-aminobenzoxazoles employing visible light photoredox catalysis under basic conditions (Scheme 1b).[12] However, most of the available methods suffer from more or less drawbacks such as expensive and/or toxic metal-based reagents requiring stoichiometric or greater amounts and cautious handling, basic conditions, elevated temperatures, long reaction times and lower yields.



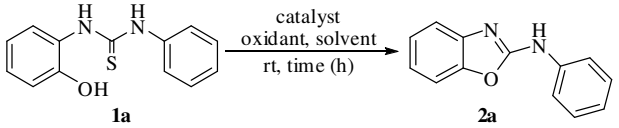
Scheme 1. Synthesis of 2-aminobenzoxazoles from *o*-phenolic thioureas.

Prompted by the above points and our continuous efforts for developing convenient and efficient heterocyclization reactions,[10a,b,12,13] we envisioned the present metal- and base-free practical synthesis of 2-aminobenzoxazoles by cyclodesulfurization of *o*-phenolic thioureas using TBAI and

H_2O_2 as a catalyst-oxidant system at room temperature (Scheme 1c).

Table1[a]

Optimization of reaction conditions[a]



1a **2a**

Entry	Catalyst (mol%)	Oxidant (2 equiv.)	Solvent	Time (h)	Yield (%)[b]
1	TBAI (1 mol%)	H_2O_2	THF	1	89
2	TBAI (1 mol%)	H_2O_2	THF	0.5	53
3	KI (1 mol%)	H_2O_2	THF	1	74
4	I_2 (1 mol%)	H_2O_2	THF	1	62
5	TBAI (1 mol%)	-	THF	2	n.d.
6	-	H_2O_2	THF	2	n.d.
7	TBAI (0.5 mol%)	H_2O_2	THF	1	60
8	TBAI (2 mol%)	H_2O_2	THF	1	89
9	TBAI (1 mol%)	TBHP	THF	1	76
10	TBAI (1 mol%)	DTBP	THF	1	n.d.
11	TBAI (1 mol%)	H_2O_2	THF	1	73[c]
12	TBAI (1 mol%)	H_2O_2	THF	1	89[d]
13	TBAI (1 mol%)	H_2O_2	CH_3CN	1	81
14	TBAI (1 mol%)	H_2O_2	C_2H_5OH	1	59
15	TBAI (1 mol%)	H_2O_2	DCM	1	76
16	TBAI (1 mol%)	H_2O_2	Et_2O	1	84

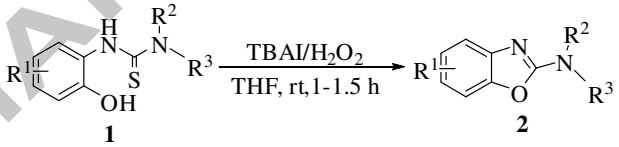
[a] Reaction conditions: *o*-phenolic thiourea **1a** (1 mmol), catalyst (1 mol%), oxidant (2 equiv.), solvent (3 mL), stirred at rt for 1-2 h. [b] Isolated yield of **2a**; n.d.= not detected, [c] 1 equiv. of H_2O_2, [d] 3 equiv. of H_2O_2.

At the beginning of our strategy, a model reaction was performed using *o*-phenolic thiourea **1a** as a substrate, TBAI as a catalyst and 30% aq H_2O_2 as an oxidant (Table 1). Gratifyingly, this metal-free catalyst and oxidant system delivered the desired product **2a** was obtained in an excellent yield (Table 1, entry 1). Initially, we set the minimum time required for the reaction and it was found to be 1 h because on decreasing the reaction time from 1 to 0.5 h, the yield was considerably reduced (Table 1, entry 1 vs 2). Next, we optimized the catalytic activity using various catalysts, such as KI, I_2 and TBAI, and it was found that TBAI was most efficient in terms of yield and time (Table 1, entry 1 vs 3 and 4). It was noted that the product **2a** was not formed in the absence of either TBAI or H_2O_2 (Table 1, entries 5 and 6). A decrease in the loading of catalyst TBAI from 1 mol% to 0.5 mol% resulted in a lower yield of the product (Table 1, entry 1 vs 7), whereas on increasing the amount of TBAI from 1 mol% to 2 mol%, there was no effect on the yield of the product (Table 1, entry 1 vs 8). Then, several oxidants (H_2O_2, TBHP and DTBP (di-*tert*-butyl peroxide) were tested and H_2O_2 was found to work most efficiently in terms of the the reaction time and yield (Table 1, entry 1 vs 9 and 10). The optimum amount of H_2O_2 was found to be 2 equiv. because the yield was decreased on decreasing its amount, but remained unchanged on using 3 equiv. (Table 1, entry 1 vs 11 and 12). Next, we screened several solvents, viz. THF, CH_3CN, C_2H_5OH, DCM, and Et_2O, and THF was found to be the best solvent (Table 1, entry 1 vs 13-16). Consequently, we arrived at the optimal reaction conditions in which **1a** (1 equiv.), TBAI (1 mol%) and H_2O_2 (2 equiv.) were stirred in THF at rt for 1 h to afford the product **2a** in 89% yield (Table 1, entry 1).

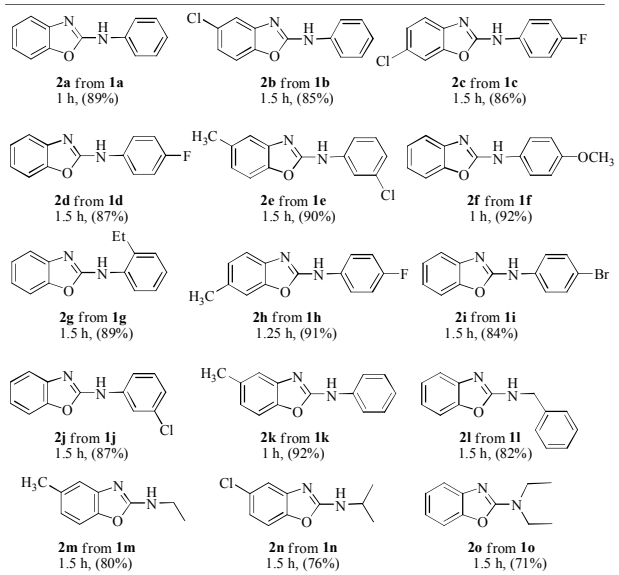
With the optimized reaction conditions in hand, we surveyed the functional group compatibility and scope of the present TBAI catalyzed synthesis of 2-aminobenzoxazoles **2** using a variety of *o*-phenolic thioureas **1** and the results are summarized in Table 2. *o*-Phenolic thioureas bearing an electron-donating or electron-withdrawing substituent generally afforded 2-aminobenzoxazoles **2** in 71-92% yields. The generality of the method was demonstrated across various kinds of structurally various shows little electronic effect of the substituents on the oxidative cyclodesulfurization reaction of *N*-substituted-2-hydroxyphenylthiourea. Interestingly, various functionalites, such as CH_3, C_2H_5, OCH_3, Br, Cl, and F, were easily tolerated to give aminobenzoxazoles **2** in excellent yields and high purity. The protocol is also suitable for phenolic thioureas bearing *N*-alkyl or *N*,*N*-dialkyl groups (Table 2, products **2m**-**2o**).

Table 2

Substrate scope for the synthesis of 2-aminobenzoxazoles from *o*-phenolic thioureas[a]



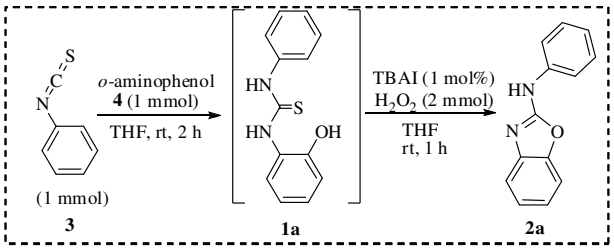
1 **2**



[a] For experimental procedure, see ref. 15.
[b] All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.[11f]
[c] Yields of isolated pure compounds **2**.

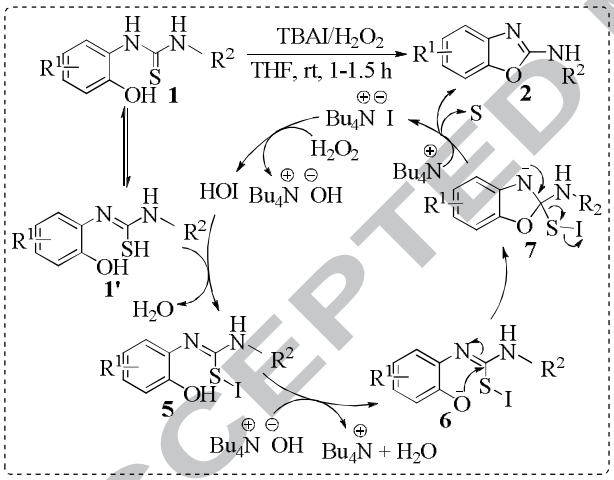
Furthermore, the method works well for a one-pot synthesis of 2-aminobenzoxazoles **2** starting directly from phenyl isothiocyanates and *o*-aminophenols (Scheme 2). Thus, we stirred a mixture of phenylisothiocyanate **3** (1 mmol) and *o*-

aminophenol **4** (1 mmol) in THF (3 mL) for 2 h at rt. After formation of the corresponding *o*-phenolic thiourea **1a**[11d] was completed (as indicated by TLC), TBAI (1 mol%) and 30% aq. H_2O_2 (2 equiv.) were added and the reaction mixture was stirred at rt for 1 h. The product **2a** was isolated in an excellent yield (80%) by usual column chromatography.[15]



Scheme 2. One-pot sequential synthesis of 2-aminobenzoxazole

On the basis of the above observations and the literature reports,[1a,d,14] a plausible mechanism for the formation of 2-aminobenzoxazoles **2** from *o*-phenolic thioureas **1** is depicted in Scheme 3. According to the proposed mechanism, tetrabutylammonium iodide reacts with hydrogen peroxide to give hypoiodite and tetrabutylamonium hydroxide. The hypoiodite reacts with the thiolic form of thiourea **1′ to** form intermediate **5**, which affords the desired product **2** through **6** and **7** with the loss of H_2O and elemental sulfur along with regeneration of the catalyst TBAI.



Scheme 3. A plausible mechanism for the formation of 2-aminobenzoxazoles

In summary, we have developed a highly efficient, metal- and base-free, operationally convenient strategy for the synthesis of 2-aminobenzoxazoles at rt. The protocol involves oxidative intramolecular cyclodesulfurization of *o*-phenolic thioureas using TBAI as a catalyst and H_2O_2 as a green oxidant. This methodology could also be exemplified for a one-pot synthesis of *N*-phenylaminobenzoxazole starting directly from *o*-aminophenol and phenyl isothiocyanate in 80% yield.

Acknowledgments

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15. *General procedure for the synthesis of 2-aminobenzoxazoles 2:* A mixture of *o*-phenolic thiourea[11d] **1** (1 mmol), TBAI (1 mol%), 30% aq. H_2O_2 (2 equiv.), and THF (3 mL) was taken in a flask and stirred at rt for 1-1.5 h (Table 2). After completion of the reaction (monitored by TLC), water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The resulting crude product was purified by silica gel chromatography using a mixture of hexane/ethyl acetate (4:1) as eluent to afford an analytically pure sample of product **2**. All the compounds **2** are known and were characterized by comparison of their spectral data with those reported in the literature.[11f] Characterization data of representative compounds **2** are given below with relevant reference:
Compound **2a**:[11f] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.04 (t, 1H, J = 7.2 Hz, ArH), 7.10 (t, 1H, J = 7.2 Hz, ArH), 7.23 (t, 1H, J = 7.2 Hz, ArH), 7.35 (t, 2H, J = 8.0 Hz, ArH), 7.42 (t, 2H, J = 8.4 Hz, ArH), 7.77 (d, 2H, J = 8.0 Hz, ArH), 10.52 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 109.32, 117.05, 118.03, 122.10, 122.56, 124.38, 129.40, 139.18, 142.89, 147.47, 158.45. MS: m/z 211 $[M+H]^+$. HRMS (FAB) Calcd for $C_{13}H_{11}N_2O$: 211.0871 $[M+H]^+$, found: 211.0875.
Compound **2d**:[11f] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05-7.18 (m, 3H, ArH), 7.21 (t, 1H, J = 7.6 Hz, ArH), 7.36 (d, 1H, J = 8.0 Hz, ArH), 7.47 (d, 1H, J = 8.0 Hz, ArH), 7.55-7.59 (m, 2H, ArH), 9.05 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.24, 115.86, 116.14, 116.72, 120.53, 120.55, 121.76, 124.37, 133.98, 141.80, 147.82, 158.88. MS: m/z 229 $[M+H]^+$. HRMS (FAB) Calcd for $C_{13}H_{10}FN_2O$: 229.0777 $[M+H]^+$, found: 229.0774.
Compound **2k**:[11f] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 6.87 (d, 1H, J = 7.6 Hz, ArH), 7.03 (t, 1H, J = 7.6 Hz, ArH), 7.24 (s, 1H, ArH), 7.32-7.39 (m, 3H, ArH), 7.78 (d, 2H, J = 8.0 Hz, ArH), 10.51 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.52, 108.72, 117.30, 117.91, 122.46, 122.68, 129.36, 133.57, 139.20, 143.05, 145.55, 158.50. MS: m/z 225 $[M+H]^+$. HRMS (FAB) Calcd for $C_{14}H_{13}N_2O$: 225.1028 $[M+H]^+$, found: 225.1024.

Highlights

- Iodide catalyzed metal- and base-free synthesis of 2-aminobenzothiazoles.
- Oxidative cyclodesufurization of *o*-phenolic thioureas to 2-aminobenzothiazoles.
- Utilization of hydrogen peroxide as a green oxidant.
- Synthesis of 2-aminobenzothiazoles directly from *o*-aminophenols and aryl isothiocyanates.