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Article

Thiourea as Bifunctional Hydrogen Bond Donor and Brønsted Base Catalyst for Green One-Pot Synthesis of 2-Aryl/Heteroaryl/Styryl Benzothiazoles in the Aqueous Medium under Ultrasound Irradiation

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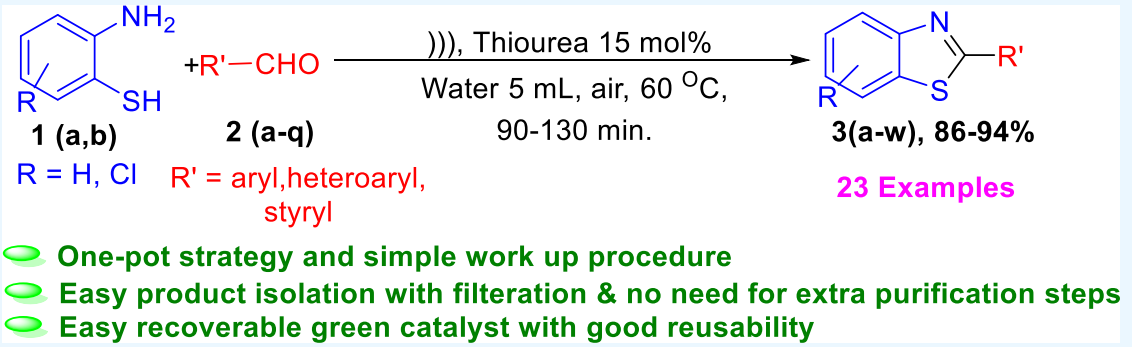

ABSTRACT: A green organocatalysis cascade strategy using thiourea in catalytic amounts as both a hydrogen bond donor and a Brønsted base bifunctional catalyst was utilized to synthesize a series of 2-aryl/heteroaryl/styryl benzothiazole derivatives. This strategy involved an ultrasound-irradiated one-pot two-component reaction between substituted aldehydes and 2-amino thiophenols in an aqueous medium at 60 °C, using air as an oxidant. At the gram-scale, this protocol yielded 87% of the desired product, making it suitable for production at a larger scale. This green and mild protocol offers excellent yields, cost-effectiveness, atom economy, step economy, and a simple operation that does not require extra purification steps. Furthermore, the catalyst is easily recoverable and can be used for up to five cycles without a significant loss of any activity.

INTRODUCTION

Thiourea and its derivatives are emerging as significant players in organocatalysis as they can form strong hydrogen bonds that activate the substrates[1,2] and can also act as Brønsted bases[3] and Brønsted acids[4,5] to promote organic transformations. Several organic reactions like Diels−Alder condensation,[6] Claisen rearrangements,[7] Pictet−Spengler reaction,[8] Strecker reaction,[9] Mannich reaction,[10,11] cyanosilylation of ketones,[12] Michael addition,[13,14] Baylis−Hillman reaction,[15−17] sulfoxide allylation,[18] nitrone TMSCN addition,[19] hydrophosphonylation,[20] reductive amination,[21] acetalization of carbonyl compounds,[22] and so forth have been reported to be catalyzed by thiourea and its derivatives.

Subsequently, thiourea derivatives have been developed to promote asymmetric organic transformations.[23] Such developments led to the introduction of more hydrogen bond donor functionalities that can activate the substrates and stabilize transient ionic species or transition states, making the pathway kinetically more advantageous. To further broaden the catalytic scope of thiourea, derivatives were designed to induce bifunctionality so that these derivatives could also act as either Brønsted acids or Brønsted bases along with being hydrogen bond donors. Key sites of hydrogen bond donation and bifunctionality of representative thiourea derivatives used by Schreiner and Takemoto are illustrated in Figure 1.

Among all of these reported and ongoing enhancements, the exploration of catalytic abilities of unsubstituted thiourea was overlooked and thus remains limited. Hence, we tried to explore the ability of unsubstituted thiourea to act as a bifunctional catalyst that can act as both a hydrogen bond donor and a Brønsted base.

For this purpose, we chose 2-aryl/heteroaryl/styryl benzothiazole derivatives as target compounds. 2-Substituted benzothiazoles are significant structural motifs that have garnered tremendous attraction in medicinal chemistry and

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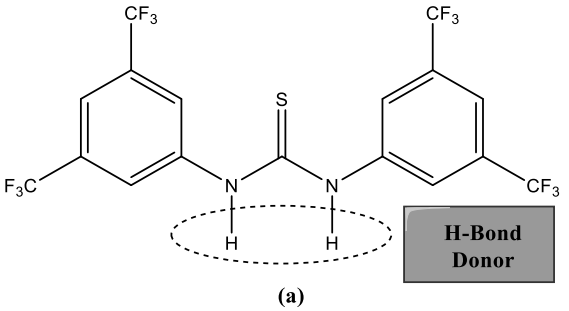
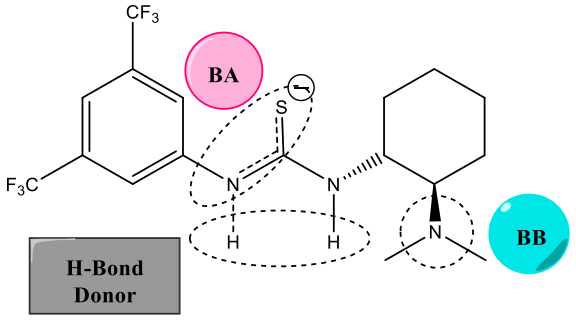


(a)

Symmetrical H-bond donor Schreiner's thiourea[24]



(b)

Bifunctional Takemoto's thiourea[25] as H-bond donor and Bronsted Acid/ Base.

Figure 1. Depiction of the key sites of hydrogen bond donation and the bifunctionality of the thiourea derivatives. BA = Bronsted acid. BB = Bronsted base.[24,25]

pharmaceutical industries;[26−30] textile,[31] rubber,[32] and leather industries;[33] electronics;[34] as chemiluminescent agents;[35] and as photosensitizers.[36] The most used method for synthesizing 2-substituted benzothiazoles involves the direct condensation of 2-aminothiophenols with substituted aldehydes. In recent years, there has been a growing interest in developing eco-friendly strategies to make this method more sustainable.[37−52] Despite efforts to improve this method, the existing approaches still possess certain limitations such as the utilization of acids, bases, toxic organic solvents, or the involvement of expensive transition metal catalysts with ligands, prolonged reaction times, high temperatures, reduced yields, lack of large-scale transposition, generation of waste products, and the requirement of complex purification steps and techniques.

To counter these problems, first we needed a technique that could replace conventional heating so that the reaction could be accelerated at low temperatures. We believed that ultrasound irradiation could be the optimal solution as sonication significantly reduces particle size and enhances mass and heat transfer, surpassing the effectiveness of conventional heating methods.[53] Second, our concern was to find a catalyst that is cost-effective, nontoxic, and able to function under mild reaction conditions to carry out direct condensation of 2-aminothiophenols with substituted aldehydes using water as a solvent and air as an oxidant.

The proposed mechanisms from previous reports revealed that two major steps were involved in the direct condensation of 2-aminothiophenols and substituted aldehydes. First, the $-NH_2$ group of 2-aminothiophenol attacks the electrophilic carbonyl group of the aldehyde to form an imine intermediate, and second, cyclization occurs leading to C−S bond formation. We decided to explore the use of thiourea as a catalyst because we knew that the thiourea could easily catalyze the first step as it is a strong hydrogen bond donor that can easily activate the carbonyl group of aldehydes and hence facilitate the attack of the $-NH_2$ group of 2-aminothiophenol to form the imine intermediate. However, to catalyze the second step, the thiourea must act as a bifunctional catalyst where on the one hand it can abstract hydrogen from the −SH group of the imine intermediate as a Brønsted base and on the other hand can provide hydrogen to the nitrogen of imine intermediate that could finally result in C−S bond formation and cyclization. We believe that thiourea can behave as a bifunctional hydrogen bond donor and Brønsted base catalyst in aqueous medium because of its structural and mesomeric tautomerism[54] (Figure 2).

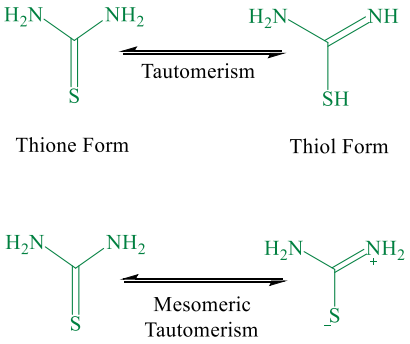


Figure 2. Tautomers of thiourea.

Due to the difference in pK_a values, the =NH group of the thiol tautomer of thiourea can easily abstract hydrogen from the −SH group of the imine intermediate; subsequently, its −SH group can donate hydrogen to the nitrogen of the imine intermediate, and thiourea can be stabilized by mesomeric tautomerism (Figure 3).

Based on these views, we proceeded with the direct condensation of 2-aminothiophenol with substituted aldehydes in ultrasound-irradiated aqueous medium using air as oxidant, and to our satisfaction, the reaction occurred smoothly with excellent yields under green and mild reaction conditions. This protocol was also successful at the gram-scale level and provided a yield of 87%.

Thus, in this work, we demonstrate the potential of unsubstituted thiourea to act as a hydrogen bond donor and Brønsted base bifunctional organocatalyst in the synthesis of important 2-substituted benzothiazole derivatives under ultrasound-irradiated green conditions using water as a green solvent and air as an oxidant at 60 °C. The green aspects of this protocol include excellent yields, cost-effectiveness, shorter reaction times, atom economy, step economy, mild reaction conditions, gram-scale production, good reusability, easy recovery of catalyst, and a simple operation that does not require extra purification steps.

RESULTS AND DISCUSSION

Optimization Studies for the Synthesis of Thiourea-Catalyzed 2-Phenylbenzothiazole (3a). During the optimization study for the synthesis of 2-aryl/heteroaryl/styryl benzothiazole derivatives, a reaction between 2-aminothiophenol (**1a**) and benzaldehyde (**2a**) was selected as the standard model reaction to synthesize 2-phenyl benzothiazole (**3a**) in

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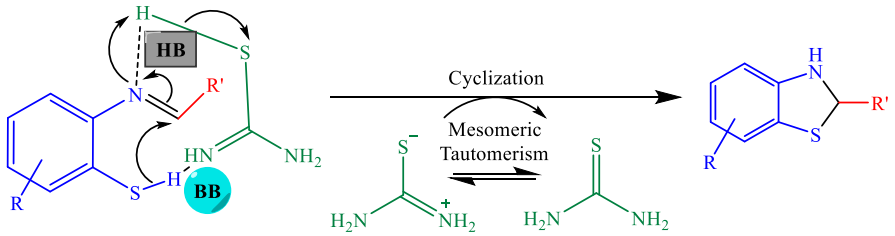
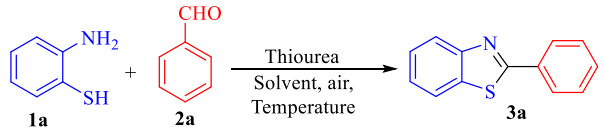


Figure 3. Probable action of thiourea as a bifunctional hydrogen bond donor and Brønsted base catalyst. HB = hydrogen bond donor. BB = Brønsted base.

the presence of air. The model reaction was carried out under different reaction conditions by using catalytic amounts of thiourea in the presence of air as an oxidant (Table 1). Initially,

Table 1. Optimization Studies for the Preparation of 2-Phenyl Benzothiazole (3a)[a]



1a 2a 3a

entry	catalyst (mol %)	solvent systems	temperature (°C)	time (hours)	yield (%)[b]
1		neat	90	10	traces
2	10	neat	90	10	traces
3	15	EtOH	RT	8	traces
4	15	H_2O	RT	8	traces
5	15	EtOH/H_2O (1:1)	RT	8	traces
6	5, 8, 12, 15, 18, 22	EtOH	reflux	6, 6, 5, 5, 5, 6	60,[c] 66,[c] 74,[c] 80,[c] 79,[c] 77[c]
7	5, 8, 12, 15, 18, 22	H_2O	reflux	5, 5, 4.5, 3, 3.5, 3.5	72,[c] 86, 87, 91, 90, 90
8	15	EtOH/H_2O (1:1)	reflux	4	81[c]
9	15	EtOH/H_2O (1:2)	reflux	4	82[c]
10	15	sonication, H_2O	30	1.5	89
11	**15**	**sonication, H_2O**	**60**	**1.5**	**93**
12	15	sonication, H_2O	90	1.5	92
13	10	sonication, H_2O	30	1.5	72[c]
14	10	sonication, H_2O	60	1.5	77[c]
15	18	sonication, H_2O	30	1.5	88
16	18	sonication, H_2O	60	1.5	91

[a]Reaction conditions: 2-aminothiophenol (1.0 mmol), benzaldehyde (1.0 mmol), solvent (5 mL), and catalytic amount of thiourea. [b]Yields are associated with isolated products. [c]Reactions were not complete.

the model reaction was performed in a catalyst- and solvent-free environment, and later, using the catalyst in the absence of any solvent. Both conditions resulted in trace amounts of the product (**3a**) (Table 1, entries 1 and 2). The model reaction was then carried out in a variety of solvent systems with varied amounts of thiourea. No significant outcomes were obtained on treating the reaction mixture at room temperature (RT) in water, ethanol, and a mixture of H_2O/ethanol in a 1:1 ratio using different mol % of thiourea (Table 1, entries 3, 4, and 5). Refluxing the reaction mixture in ethanol and in a mixture of H_2O/ethanol of 1:1 ratio and 2:1 ratio gave moderate to good yields, depending upon different mol % of thiourea but the reactions were not complete (Table 1, entries 6, 8, and 9). In continuation, refluxing the reaction mixture in water gave good results, and most of the reactions were complete (Table 1, entry 7). However, to make the protocol greener by lowering the temperature requirements and by shortening the reaction time, we tried this reaction under ultrasound irradiation (Table 1, entries 10−16). To our delight, we achieved the best results under ultrasound irradiation in the presence of 15 mol % (0.011 g) of thiourea using water as solvent and air as oxidant at 60 °C (Table 1, entry 11).

Thiourea Catalyzed Synthesis and Substrate Scope of 2-Aryl/Heteroaryl/Styryl Benzothiazoles in the Aqueous Medium under Ultrasound Irradiation. After optimization (Table 1), a variety of aromatic, heteroaryl, and styryl aldehydes with electron-donating and electron-withdrawing groups and substituted 2-aminothiophenols were used to synthesize 2-substituted derivatives of the target compound (Scheme 1). In every case, the reactions were complete in excellent yields and within the indicated reaction durations. No notable substituent effect of the various aldehydes or 2-aminothiophenols was detected in these reactions, and the results for the synthesized compounds corresponded with reported literature data (see Supporting Information).

After successfully testing the representative procedure on the mmol scale, we scaled up the reaction to gram quantities for the synthesis of **3a** and obtained a yield of 87% (Scheme 2).

Reusability and Recovery of the Catalyst. The model reaction from Table 1, entry 11 was chosen to examine the reusability of thiourea. The model reaction was repeated 5 times using the filtered aqueous solution of the previous run without introducing any additional catalyst in the following run. According to the results obtained, thiourea can be reused for up to five cycles without any significant loss in catalytic activity, as the yield of the product and the time needed for the reaction were not substantially affected (Figure 4). We also managed to recover the catalyst in the last run, by evaporating the water and recrystallizing it in ethanol. After the fifth run, the catalyst recovery was 90%. The purity of the recycled catalyst was validated by comparing the IR and PXRD spectra of fresh and recycled thiourea (Figure 5).

Mechanism. The possible mechanism of this work catalyzed by thiourea in an aqueous medium is illustrated in Scheme 3. Here, the thiourea shows bifunctionality by acting as a hydrogen bond donor and Brønsted base. As a hydrogen bond donor, it activates the carbonyl group of substituted aldehydes (**2a−q**) and facilitates the attack of the $-NH_2$ group of the 2-aminothiophenol (**1a−b**) on the activated carbonyl

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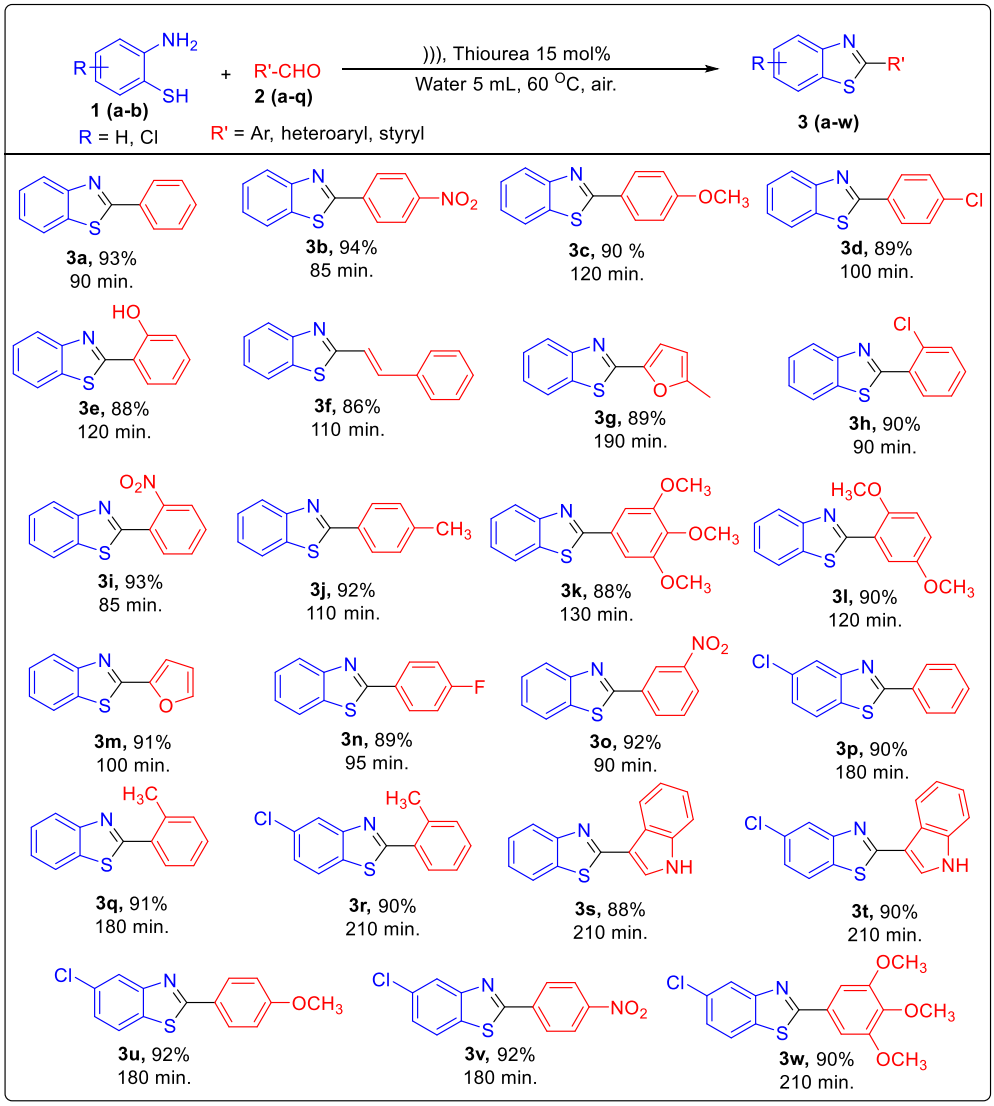
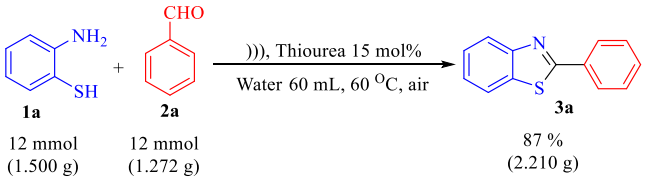
Scheme 1. Synthesis and Substrate Scope of 2-Substituted Benzothiazole Derivatives 3(a−w)[a]



[a]Yields are associated with isolated products.

Scheme 2. Gram-Scale Synthesis of 3a



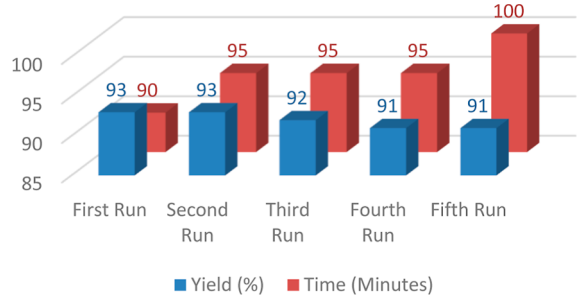


Figure 4. Reusability of thiourea for a standard model reaction.

carbon of the aldehyde, thus, leading to the formation of the imine intermediate (**2′**) after losing a molecule of water. Then, the tautomeric thiol form of thiourea acts as a Brønsted base and possibly forms a transition state (TS-I) with **2′** where it abstracts a hydrogen from the −SH group of the intermediate and undergoes cyclization forming intermediates **3′**. The thiourea is believed to be stabilized by mesomeric tautomerism. Finally, under the reaction conditions, intermediate **3′** undergoes aromatization by oxidation with oxygen in air to furnish the desired products **3(a−w)**.

Further, to confirm that thiourea can act as a Brønsted base and can abstract hydrogen, we ran two control reactions where we used 2-aminophenol (**1′**) and benzene-1,2-diamine (**1″**) as starting material. It was found that the reaction did not proceed beyond the formation of the imine intermediate, and it can be ascribed to the fact that it is difficult to abstract hydrogen from the atoms having more or equivalent electronegativity and larger pK_a values as in the case of **1′** and **1″**, respectively (Scheme 4). These results validate the idea of thiourea acting as a Brønsted base and abstracting hydrogen from the less electronegative −SH group of 2-

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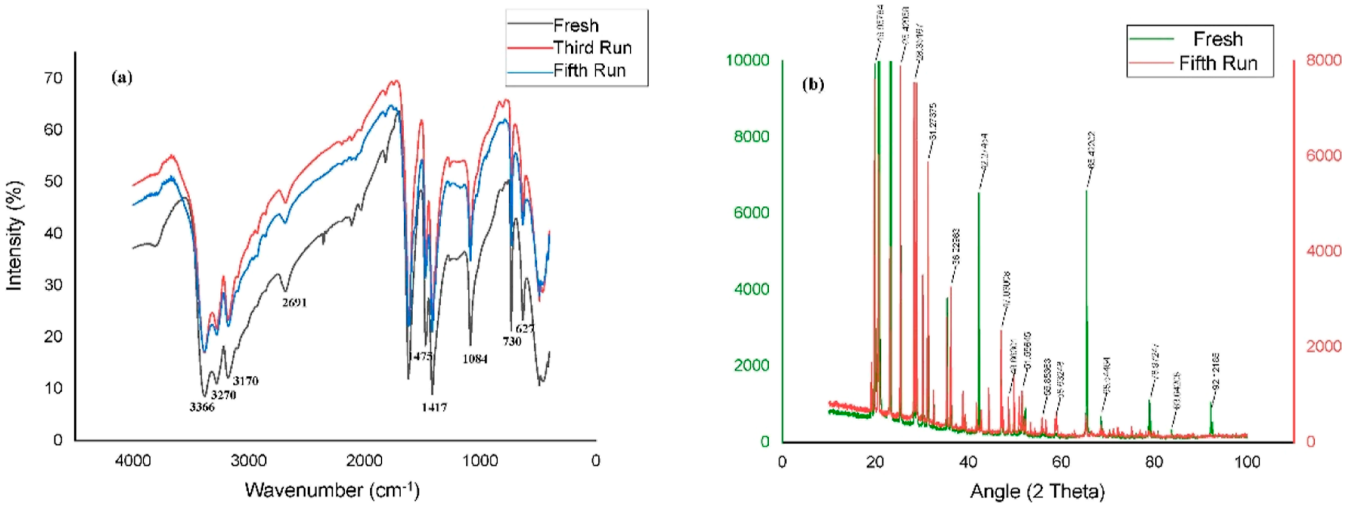
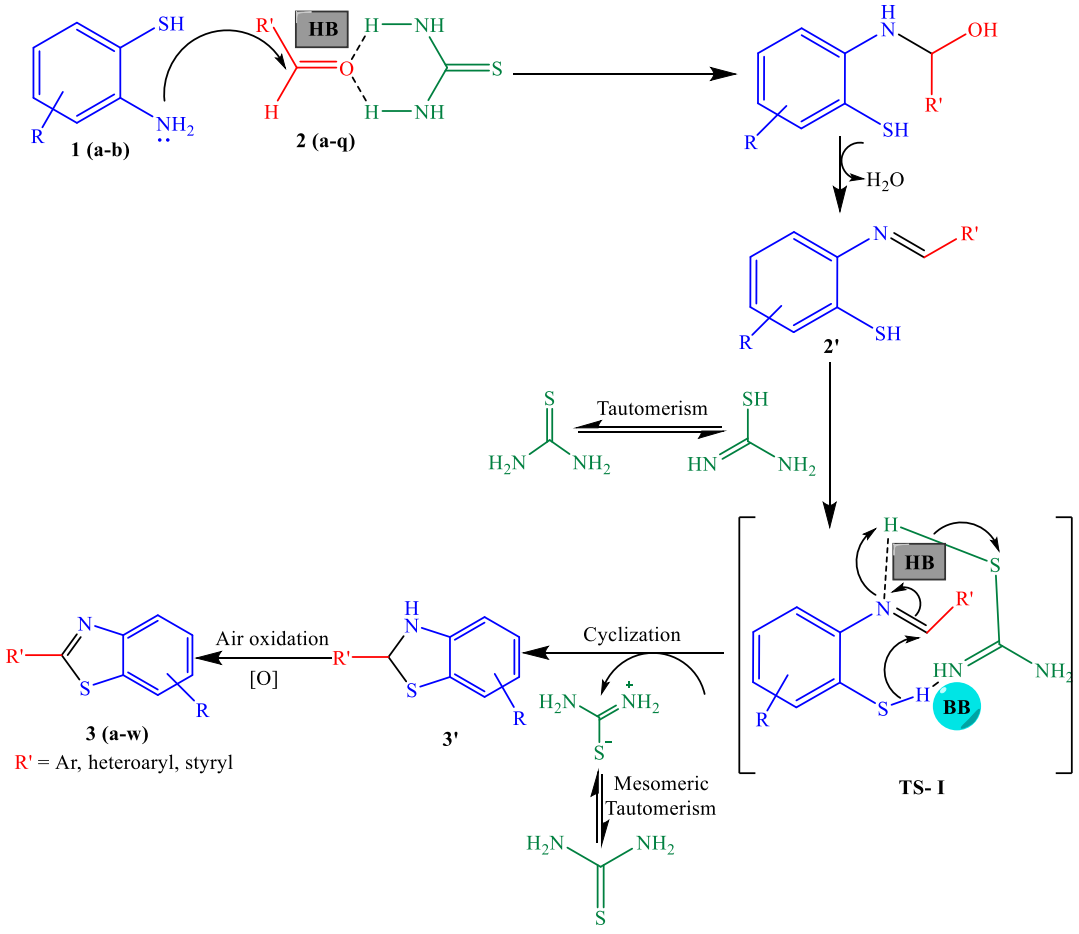


Figure 5. Comparative studies of fresh thiourea and recycled thiourea. (a) IR spectra of fresh thiourea (black) and thiourea after the third run (red) and fifth run (blue); (b) PXRD spectra of fresh thiourea (green) and thiourea after the fifth run (red).

Scheme 3. Possible Mechanism for the Synthesis of 2-Aryl/Heteroaryl/Styryl Benzothiazole Derivatives (3a−w)



aminothiophenol because if this was not the case then the control reactions would also have generated desired 2-substituted benzoxazole and 2-substituted benzimidazole.

Finally, to demonstrate that oxygen in the air facilitates the final conversion of intermediate **3′** to product **3a**, two parallel experiments were conducted under different environments using the optimized reaction conditions (Table 2). One experiment was carried out in the presence of air, while the other was performed under a nitrogen environment with degassed solvent. Results indicate that 2-substituted benzothiazole **3a** was obtained only in traces under the nitrogen atmosphere while the intermediate **3′** was produced with a yield of 58% (Table 2, entry 1). However, when the reaction was performed in the presence of air, product **3a** was obtained in a yield of 93%, and intermediate **3′** was found in traces (Table 2, entry 2). Therefore, it can be concluded that oxygen

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ACS Omega 2024, 9, 8343−8351

Scheme 4. Control Reactions to Check Thiourea Can Act as a Brønsted Base

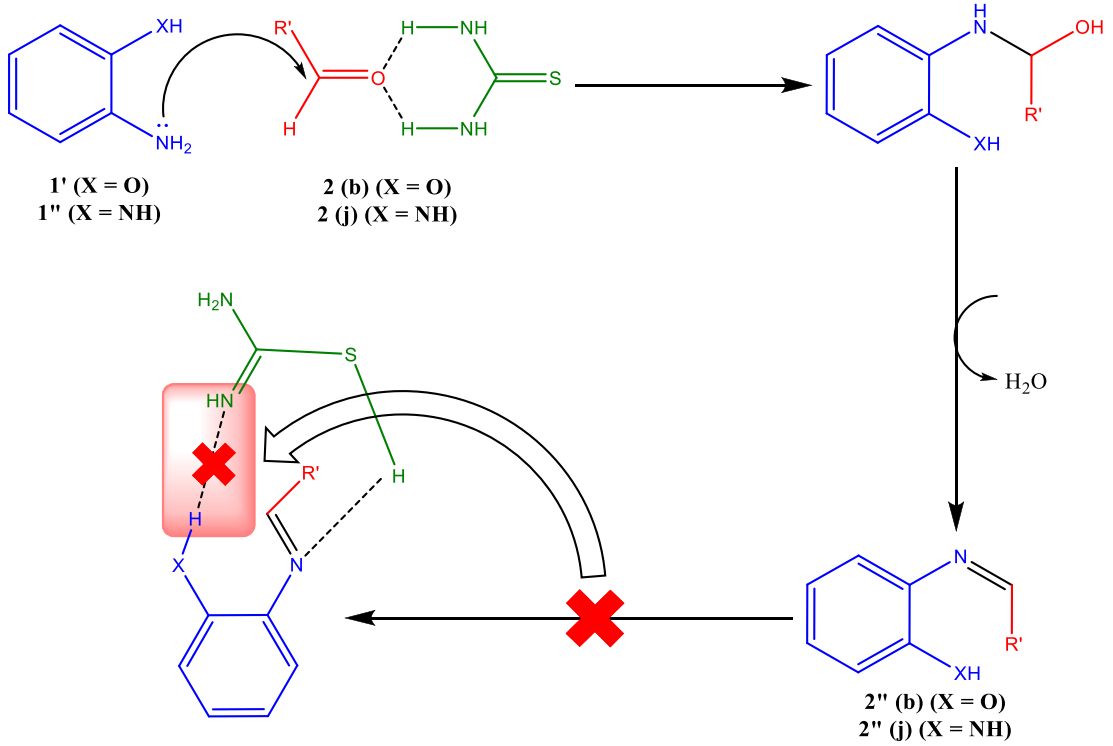
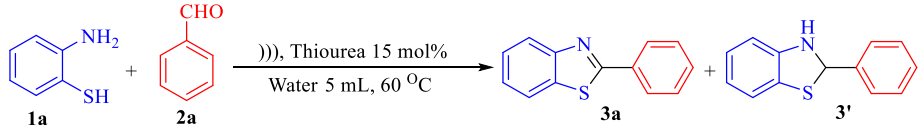


Table 2. Control Experiments Showing the Effect of Atmosphere in the Formation of (3a)[a]



entry	thiourea (mol %)	atmosphere	yield (%)[b]	
			3a	3′
1	15	nitrogen (degassed solvent)	traces	58
2	15	air	93	traces

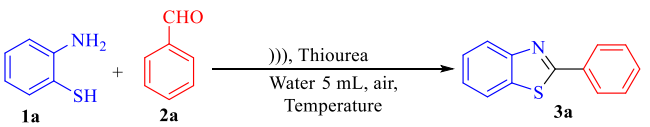
[a]Reaction conditions: 2-aminothiophenol (1.0 mmol), benzaldehyde (1.0 mmol), solvent (5 mL), and catalytic amount of thiourea. [b]Yields are associated with isolated products.

in the air acts as an oxidant to promote the transformation of 3′ to product **3a**.

Role of Ultrasonic Irradiations in Rate Acceleration at Lower Temperature. Ultrasonic energy has been found to be an effective means of accelerating chemical reactions, primarily through the generation of cavitation bubbles. These bubbles act as microreactors, creating high temperatures of more than several thousand degrees and pressures greater than 1000 atmospheres. Such conditions can dramatically increase the rate of a reaction, making ultrasonic energy a valuable tool in many industrial and scientific applications.[52] During ionic reactions between liquid and solid substances, bubbles may form near or at the solid surface. When these bubbles implode, a powerful liquid jet is directed toward the surface, disturbing interfacial boundary layers, and significantly enhancing mass and heat transfer. Additionally, the implosion of bubbles can create shock waves that trigger changes in pressure, temperature, and mechanical behavior.[55] Furthermore, cavitation can decrease particle size, enhancing surface mass transfer.[53] Now, to determine which factors are most crucial in this sonication-promoted synthetic procedure, we conducted some experiments using optimized conditions (Table 3).

To determine the impact of thiourea as a catalyst in this process, we sonicated 2-aminothiophenol **1a** with benzaldehyde **2a** in a water bath without the catalyst. After 5 h, only traces of **3a** were isolated (Table 3, entry 1). The remaining

Table 3. Control Experiments to Determine the Role of Sonication in the Formation of (3a)[a]



entry	thiourea (mol %)	temperature	yield (%)[b]
1		60 °C	traces
2	15	RT	12

[a]Reaction conditions: 2-aminothiophenol (1.0 mmol), benzaldehyde (1.0 mmol), solvent (5 mL), and catalytic amount of thiourea. [b]Yields are associated with isolated products.

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ACS Omega 2024, 9, 8343−8351

material remained unreacted, indicating that sonication alone cannot complete this transformation, and thiourea as a catalyst is required for the formation of **3a**. Next, the reaction was carried out in an ultrasound water bath at RT, and **3a** was obtained with a yield of 12% (Table 3, entry 2). This indicates that high temperatures and pressures play a crucial role and mechanical effects are not the sole cause of rate enhancement. Moreover, the required temperature in sonication is much lower than that in conventional heating (see Table 1, entry 7) making it a more sustainable process.

Dynamic light scattering (DLS) analysis was used to determine the particle size distribution of both commercial and water-bath sonicated thiourea. The results indicated that the ultrasound-bath sonicated catalyst had smaller particles and a narrower range of particle sizes (ranging from 220 to 295 nm with PDI 0.576) compared to the commercial thiourea (ranging from 712 to 955 nm with PDI 0.960) (Figure 6). This difference in particle size suggests that sonication reduces the particle size, which, in turn, makes the catalyst more efficient and leads to faster reaction times.

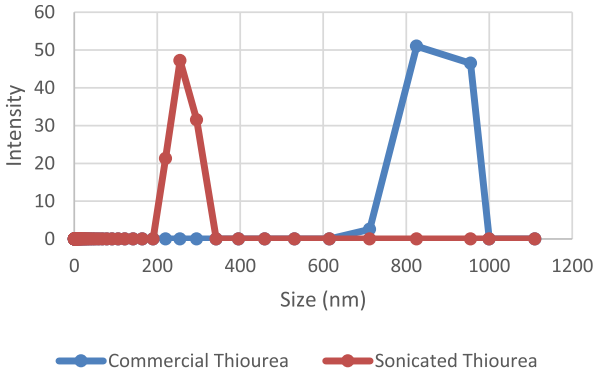

Figure 6. Particle distribution analysis of sonicated and commercial thiourea.

EXPERIMENTAL SECTION

General Information. All substituted aldehydes, 2-aminothiophenol, and thiourea were purchased from commercial suppliers and used without further purification. The progress of the reaction was monitored by thin layer chromatography (TLC) on Merck silica gel 60-F-254 aluminum plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III HD 500 MHz instrument using $CDCl_3$ as solvent. Melting points were determined in open capillary tubes and were uncorrected. FTIR spectra were recorded by using a KBr disc on a Bruker ALPHA analyzer. Mass spectra were recorded on a Xevo G2-S Q Tof (Waters, USA) mass spectrometer (direct mass ESI-APCI). Powder XRD was recorded on PANalytical EMPYREAN diffractometer. The ultrasonic irradiation was carried out in an Axiva-ultrasonic bath-XUB digital, model XUB10, ultrasonic power 200 W, operating frequency 32 kHz, with a working capacity of 9.5 L having a mechanical timer (60 min with continuous hold) and supply voltage 230 V. DLS analysis for particle size distribution was recorded on Zetasizer Nano ZSP (ZEN 5600).

General Procedure for the Synthesis of 2-Aryl/Heteroaryl/Styryl Benzothiazole Derivatives. In a 25 mL round-bottomed flask, a mixture of aldehyde (1.0 mmol), 2-aminothiophenol (1.0 mmol), and thiourea (0.011 g, 15 mol %) in water (5 mL) was treated at 60 °C on the sonicator for the indicated time. Once the reaction completed [as monitored by TLC (ethyl acetate/*n*-hexane 1:9)], sonication was stopped, and 10 mL of water was added. Then the reaction mixture was stirred for 5 min at RT, and during this time, the product precipitated and was subsequently separated by filtration. The separated product was washed several times with water. After drying, a pure product was obtained. Further purification or the addition of an organic solvent was not required. The catalyst was dissolved in the filtrate and, hence, separated from the product. Finally, water was evaporated from the filtrate to recover the thiourea, which was later recrystallized with ethanol.

Spectral Details. *2-Phenylbenzo[d]thiazole (**3a**).* Yellow solid. Yield: 0.196 g, 93%; R_f = 0.48 (ethyl acetate/*n*-hexane 1:9); mp: 112−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS, δ, ppm): 8.13−8.09 (m, 3H), 7.90 (d, J = 7.9 Hz, 1H), 7.50 (m, 4H), 7.39 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 168.2, 154.2, 135.1, 133.7, 131.1, 129.1, 127.7, 126.4, 125.3, 123.3, 121.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_9NS + H^+$, 212.0528; found, 212.0527.

CONCLUSIONS

We demonstrated the potential of unsubstituted thiourea as a bifunctional organocatalyst that can act as both a hydrogen bond donor and Brønsted base to synthesize significantly important 2-aryl/heteroaryl/styryl benzothiazole derivatives under ultrasound-irradiated green conditions using water as the green solvent and air as an oxidant at 60 °C. The other green features of this protocol are a one-pot strategy, high yields, low costs, shorter reaction time, good atom and step economies, good reusability of the catalyst for up to five cycles without losing any remarkable catalytic activity, easy recovery of catalyst by filtration, and a straightforward process that does not require additional purification methods.

Hence, the reported work is advantageous and could be further utilized to explore the catalytic potential of unsubstituted thiourea in different organic transformations and to accomplish sophisticated therapeutic frameworks in a one-pot fashion.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c09164.

Supporting Information includes detailed experimental procedures; a comparison table between existing literature reports and the current work; and ^{1}H NMR, ^{13}C NMR, and mass spectral details of synthesized compounds (PDF)

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Author Contributions

K.S. performed the experiments, gathered funding, and collected the needed literature; Manju, A.K.R., and N.J. performed a supporting role in the collection of the needed literature; A.G. conceptualized the experiment, worked on methodology, wrote the complete manuscript, characterized the data, and supervised the experimental work. Finally, all the authors have given approval to the final version of the manuscript and the Supporting Information.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

RT, room temperature; TS I, transition state I; TLC, thin layer chromatography

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