

Simple Synthesis of Benzothiazole and Benzothiazoline Compounds Using Cyanuric Chloride as Catalyst

Chomchai Suksai, Thanida Trakulsujaritchok, Jaray Jaratjaroonphong,
Manassawee Janrod and Uthaiwan Sirion^{*}

Department of Chemistry, Faculty of Science, Burapha University, Thailand

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Abstract

Background and Objectives: The synthesis of benzothiazole and benzothiazoline derivatives, crucial heterocyclic compounds widely applied in pharmaceuticals and materials science has attracted increasing interest due to their diverse biological and chemical properties. These compounds exhibit antibacterial, anticancer, and antioxidant activities, as well as important optical and electronic features, making them valuable for various applications in medical and industrial fields. Traditional synthetic routes for these compounds, however, often involve toxic reagents, expensive catalysts, and harsh reaction conditions that generate significant chemical waste and pose environmental and safety risks. For instance, the use of metal-based catalysts and hazardous solvents in conventional methods increases the environmental footprint and costs of production. As a result, there is a pressing need to develop alternative, sustainable, and environmentally friendly approaches for the synthesis of these compounds. Therefore, this study aims to develop a green and efficient synthetic approach for the synthesis of benzothiazole and benzothiazoline derivatives. Cyanuric chloride, a non-toxic, low-cost catalyst, was selected as a highly efficient catalyst. The use of water, an environmentally benign solvent was explored as a reaction medium, in comparison to organic solvents. The influence of various aldehyde substrates, particularly those bearing electron-donating and electron-withdrawing groups, on the yield of the desired products was also investigated. This study explores the optimization of reaction parameters and the application of green chemistry principles in heterocyclic synthesis, with the goal of achieving high yields of the target compounds under mild conditions.

Methodology: The synthetic approach employed in this study involved the reaction of 2-aminothiophenol with a range of aldehydes, including aliphatic, aromatic, and heterocyclic aldehydes, in a 1:1 molar ratio. Cyanuric chloride was used as the catalyst for the Friedel-Crafts cyclocondensation reaction. A systematic investigation was conducted to optimize the reaction such as catalyst loading, type and volume of solvent, reaction time, and reaction temperature. The optimization process involved the reactions under mild conditions, typically at room temperature.

Both water, as a green solvent, and a variety of organic solvents with different polarities were evaluated. Water was chosen for its low environmental impact, as it is non-toxic, abundant, and inexpensive. Several organic solvents were investigated, including polar protic solvents such as methanol and ethanol, polar aprotic solvents such as tetrahydrofuran, dimethylformamide, and 1,4-dioxane, non-polar solvents such as 1,2-dichloroethane, acetonitrile, and toluene as well as an ionic liquid ([bmim][Br]). The reactions were monitored using thin-layer chromatography (TLC), and the product was confirmed by nuclear magnetic resonance (NMR) spectroscopy.

Main Results: The reaction successfully yielded both benzothiazole and benzothiazoline derivatives in yields ranging from 22% to 98%, depending on the aldehyde type and solvent used. Notably, aldehydes with electron-donating groups such as methyl and methoxy substituted aromatic aldehydes led to higher yields of benzothiazole derivatives. On the other hand, aldehydes with electron-withdrawing groups such as nitro or carbonyl functional groups tended to favor the formation of benzothiazolines, albeit in moderate yields. These results suggest that electron-donating groups enhance the nucleophilicity of the aldehydes, thereby facilitating the cyclocondensation reaction. A key finding of this study was that water, when used as the solvent, performed comparably or even better than conventional organic solvents, demonstrating its viability as a green solvent for this reaction. In some cases, water even provided higher yields of the desired products. This result supports the concept of green chemistry, where water can be used as a sustainable alternative to toxic and expensive organic solvents. The reactions proceeded smoothly at room temperature, and no additional heating or the use of hazardous reagents was required, further enhancing the eco-friendly nature of the approach. Catalytic efficiency was also evaluated using various catalysts, including cyanuric chloride, dodecyl benzenesulfonic acid (DBSA), and iron(III) chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$). The study confirmed that cyanuric chloride was the most efficient catalyst for this reaction, affording higher yields of the desired products. In contrast, control reactions conducted without any catalyst produced significantly lower yields, indicating the essential role of cyanuric chloride in facilitating the cyclocondensation. The reaction time and solvent volume were identified as crucial factors in determining the yield and stability of the products. Prolonging the reaction time to 6.0 hours resulted in reduced yields and signs of product degradation, while shortening the reaction time to 1.0 hour led to incomplete conversion of the reactants. Similarly, reducing the water volume to 1.0 mL led to lower yields, likely due to an increase in the acidity of the reaction medium, which negatively impacted the reaction efficiency. These findings emphasize the importance of optimizing reaction conditions for achieving high yields of the desired products.

Conclusions: This study demonstrates that cyanuric chloride (TCT) is an effective and efficient catalyst for the synthesis of benzothiazole and benzothiazoline derivatives through Friedel-Crafts cyclocondensation of 2-aminothiophenol with a variety of aldehydes. The reaction was successfully optimized under mild conditions, with both water and 1,4-dioxane as optimal solvents. The reaction proceeded smoothly at room temperature, thus confirming the eco-friendly nature of the approach. The developed protocol, which utilizes cyanuric chloride and water as a catalyst and solvent, respectively, aligns with the principles of green chemistry, including the reduction of chemical waste, low energy consumption, and minimized environmental impact. The substrate scope analysis indicated that the method is broadly applicable to a wide range of aldehydes, with aromatic aldehydes, particularly those with electron-donating substituents, leading to high yields of benzothiazole derivatives. In contrast, aldehydes with electron-withdrawing groups favored the formation of benzothiazolines. This study not only provides a sustainable, low-cost, and safe method for the synthesis of benzothiazole and benzothiazoline derivatives but also contributes to the development of green synthetic routes in organic chemistry. The findings of this research provide a strong foundation for future work on sustainable heterocyclic synthesis and offer a promising avenue for large-scale industrial applications, where both safety and environmental impact are critical considerations.

Keywords : simple synthesis ; benzothiazole ; benzothiazoline ; cyanuric chloride ; 2-aminothiophenol

*Corresponding author. E-mail : uthaiwan@buu.ac.th

Introduction

Benzothiazoles are an important class of heterocyclic compounds, widely utilized in the synthesis of pharmaceuticals (Chhabra *et al.*, 2016; Khokra *et al.*, 2011; Gupta & Rawat, 2010), natural products (Blunt *et al.*, 2016), and as precursors for the preparation of functional materials (Ji & Shi, 2006; Rodionov *et al.*, 2007). Numerous of benzothiazole derivatives have been reported to exhibit a wide range of biological activities, for examples anti-cancer (Marsilje *et al.*, 2003; Ali *et al.*, 2020), anti-microbial (Gupta *et al.*, 2022), anti-inflammatory (Kumar & Singh, 2021; Gupta *et al.*, 2022), anti-viral activities (Asiri *et al.*, 2020), antibacterial (Kashyap *et al.*, 2023) (Figure 1).

Numerous studies have reported the synthesis of benzothiazole derivatives *via* Friedel-Crafts acylation reactions, employing a variety of catalysts such as solid heteropoly acid supported on silica gel ($\text{Cu}_{3/2}\text{PMo}_{12}\text{O}_{40}/\text{SiO}_2$) (Fazaeli, & Aliyan, 2009), Amberlite IR-120 (Pasha, & Nizam, 2012), ZnBr_2/ABM (Riadi *et al.*, 2011), $\text{Pt}/\text{Al}_2\text{O}_3$ or

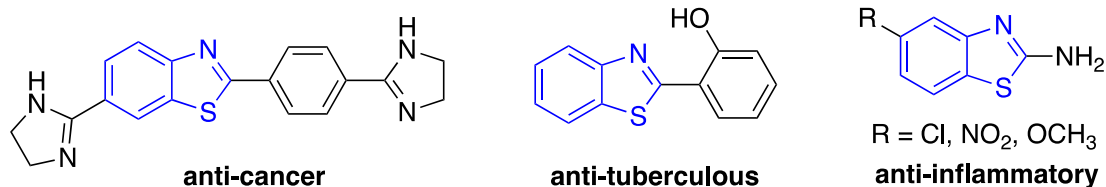


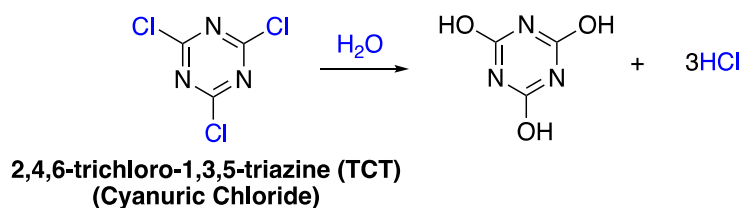
Figure 1 Examples of benzothiazole derivatives and their exhibit biological activities.

Pt/TiO₂ (Chaudhari *et al.*, 2015), yttrium (III) chloride (YCl₃) (Fan *et al.*, 2015), *p*-toluenesulfonic acid (pTsOH) (Kumar *et al.*, 2011), H₂O₂/HCl (Guo *et al.*, 2009), L-proline (Lee *et al.*, 2012), ceric ammonium nitrate (CAN) (Al-Qalaf *et al.*, 2008), Brønsted acid catalyzed (Mayo *et al.*, 2014), triphenyl tetrabutylammonium bromide (Meghdadi *et al.*, 2012), Fe₃O₄@SiO₂/collagen (Ghafuri *et al.*, 2016) and CuO nano-particles supported on silica (Inamdar *et al.*, 2013). However, these methods often present significant limitations, including the requirement for high reaction temperatures, the use of costly and toxic catalysts, and complicated experimental procedures (Kim *et al.*, 2011). In some cases, microwave irradiation is also necessary (Fazaeli & Aliyan, 2009; Pasha, & Nizam, 2012). These drawbacks have motivated us to develop a more efficient, economical, and environmentally friendly method for synthesizing benzothiazole derivatives.

At present, the sustainable and environmentally benign chemical processes have become a major focus in the field of organic synthesis. Green chemistry aims to reduce or eliminate the use and generation of hazardous substances through the design of safer, more efficient methods. Within this context, the development of high-performance catalysts that are non-toxic, cost-effective, stable, and reusable is of great importance. Such catalysts not only minimize environmental impact but also offer economic advantages by reducing waste and operational costs. Among the various approaches in green synthesis, metal-free catalytic systems have attracted significant attention due to the growing concerns over the toxicity and high cost of transition metals. Moreover, metal contamination is particularly problematic in the pharmaceutical industry, where the removal of trace metal residues is both challenging and costly. Therefore, the development of practical and metal-free reactions offers a promising approach toward achieving cleaner and more sustainable chemical processes.

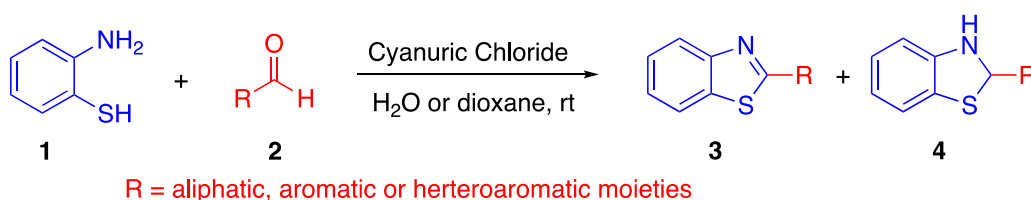
2,4,6-Trichloro[1,3,5]triazine, commonly known as cyanuric chloride (TCT), is a commercially available and inexpensive organic compound that appears as a white crystalline solid, with a melting point of 146 °C and a density of 1.32 g/cm³. It is stable, non-volatile, inexpensive, non-toxic, and safe to handle, making it suitable for use as an environmentally friendly catalyst. Cyanuric chloride typically generates hydrochloric acid (HCl) in the presence of

moisture and is widely used as an acid catalyst (Scheme 1). To date, cyanuric chloride has been successfully employed as a catalyst in the synthesis of various organic compounds such as 14-aryl or alkyl-14-*H*-dibenzo[*a,j*]xanthenes (Bigdeli *et al.*, 2007), benzo[1,3]dioxane (Li *et al.*, 2011), amidoalkyl naphthols (Mahdavinia, & Bigdeli, 2009), Fischer indoles (Siddalingamurthy *et al.*, 2013), 5-substituted-1*H*-tetrazoles (Sivaguru *et al.*, 2015), and 2,4,6-triarylpyridines (Maleki *et al.*, 2010). Moreover, cyanuric chloride also utilized as substrates in material science (Miron & Wilchek, 2017).



Scheme 1 Structure of cyanuric chloride and its hydrolysis reaction in the presence of moisture or water

This study explores the application of cyanuric chloride as a green, metal-free catalyst in the straightforward synthesis of benzothiazole (3) and benzothiazoline (4) derivatives, emphasizing its efficiency and environmental benefits. The reaction was carried out using water or 1,4-dioxane as solvents at room temperature through the condensation of 2-aminothiophenol with various aldehydes, including aliphatic, aromatic, and heteroaromatic aldehydes (Scheme 2)



Scheme 2 Synthetic methods for the synthesis of benzothiazoles (3) and benzothiazolines (4)

Methodology

General methods: All chemicals were purchased from commercial sources and used without further purification. Proton NMR spectra were recorded using a BRUKER AVANC (400 MHz) spectrometer from Burapha

University. All spectra were measured in CDCl_3 solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethyl silane (δ 0.00) or chloroform (δ 7.26). Column chromatography was carried out using open-column chromatography utilized silica gel 60-7734 and eluting with EtOAc/n-hexane. Thin layer chromatography (TLC) was performed with Merck silica gel 60 PF254 aluminum plate. Melting points were measured using a melting point apparatus (Griffin) from Burapha University.

Synthesis of benzothiazole derivatives 3: A mixture of aldehyde **2** (1.00 mmol) and cyanuric chloride (TCT) (5 mol%, 9.22 mg) in water or dioxane (3.0 mL) was added 2-aminothiophenol **1** (1.00 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over sodium sulfate anhydrous and concentrated using rotary evaporator. The crude product was purified by column chromatography (SiO_2 , 5-20% ethyl acetate/n-hexane as eluent depend on each derivative) to give the corresponding products **3a-3j** and **4a-4j**.

2-phenyl-1H-benzothiazole (3a): $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.39 (t, 1H, J = 7.4 Hz, H-4'), 7.48-7.52 (m, 4H, H-6, H-7, H-3'), 7.91 (d, 1H, J = 8.0 Hz, H-8), 8.06-8.12 (m, 3H, H-5, H-2'); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 121.55, 123.17, 125.12, 126.24, 127.49 (2 $\times$ C), 128.95 (2 $\times$ C), 130.89, 133.55, 135.00, 154.08, 167.99.

2-(4-Fluorophenyl)-1H-benzothiazole (3b): $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.19 (t, 2H, J = 8.4 Hz, H-3'), 7.39 (t, 1H, J = 7.4 Hz, H-7), 7.50 (t, 1H, J = 7.8 Hz, H-6), 7.90 (d, 1H, J = 7.2 Hz, H-8), 8.04-8.12 (m, H-5, H-2'); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 116.07 (d, J = 22.0 Hz, 2 $\times$ C-F), 121.54, 123.13, 125.18, 126.34, 129.44 (d, J = 9.0 Hz, 2 $\times$ C-F), 134.99, 154.04, 163.13, 165.63, 166.65.

2-(4-Nitrorophenyl)-1H-benzothiazole (3c): $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.47 (t, 1H, J = 7.2 Hz, H-7) 7.56 (t, 1H, J = 7.8 Hz, H-6), 7.96 (d, 1H, J = 8.0 Hz, H-8), 8.14 (d, 1H, J = 8.0 Hz, H-5), 8.27 (d, 2H, J = 8.4 Hz, H-2'), 8.36 (d, 2H, J = 8.8 Hz, H-3').

2-(4-Hydroxyphenyl)-1H-benzothiazole (3d): $^1\text{H-NMR}$ (400 MHz, DMSO): δ 6.13 (d, 2H, J = 8.8 Hz, H-3'), 6.60 (t, 1H, J = 6.8 Hz, H-7), 6.70 (t, 1H, J = 6.8 Hz, H-6), 7.13 (d, 2H, J = 8.8 Hz, H-2'), 7.18 (d, 1H, J = 8.0 Hz, H-8), 7.28 (d, 1H, J = 7.6 Hz, H-2'), 9.43 (brs, 1H, OH); $^{13}\text{C-NMR}$ (100 MHz, DMSO- d_6): δ 116.55 (2 $\times$ C), 122.55, 122.76, 124.52, 125.35, 126.87, 129.50 (2 $\times$ C), 134.58, 154.20, 160.99, 167.92.

2-(4-Methoxyphenyl)-1H-benzothiazole (3e): $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.89 (s, 3H, OMe), 7.00 (d, 2H, J = 8.8 Hz, H-3') 7.35 (t, 1H, J = 8.0 Hz, H-7), 7.47 (t, 1H, J = 7.6 Hz, H-6), 7.88 (d, 1H, J = 8.0 Hz, H-8), 8.03 (d, 1H, J = 8.8 Hz, H-5) 8.04 (d, 2H, J = 8.8 Hz, H-2'); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 55.33, 114, 121.41, 122.72, 124.72, 126.10, 126.33, 129.01, 134.77, 154.13, 161.82, 167.76.

2-(3-Methoxy-4-hydroxyphenyl)-1H-benzothiazole (3f): ^1H -NMR (400 MHz, CDCl_3): δ 4.01 (s, 3H, OMe), 6.17 (s, 1H, OH) 7.00 (d, 1H, $J = 8.4$ Hz, H-3'), 7.36 (t, 1H, $J = 8.0$ Hz, H-7), 7.47 (t, 1H, $J = 8.4$ Hz, H-6), 7.54 (dd, 1H, $J = 2.0, 8.4$ Hz, H-2'), 7.72 (d, 1H, $J = 2.0$ Hz, H-6'), 7.88 (d, 1H, $J = 8.0$ Hz, H-8), 8.03 (d, 1H, $J = 8.4$ Hz, H-5)

2-(Pyrrol-2-yl)-1H-benzothiazole (3g): ^1H -NMR (400 MHz, CDCl_3): δ 6.31-6.34 (m, 1H, pyrrole), 6.85-6.87 (m, 1H, pyrrole), 6.95-6.98 (m, 1H, pyrrole), 7.32 (t, 1H, $J = 7.4$ Hz, H-7), 7.44 (t, 1H, $J = 7.4$ Hz, H-6), 7.83 (d, 1H, $J = 7.6$ Hz, H-8), 7.89 (d, 1H, $J = 8.0$ Hz, H-5)

2-(Furan-2-yl)-1H-benzothiazole (3h): ^1H -NMR (400 MHz, CDCl_3): δ 6.60 (dd, 1H, $J = 1.6, 3.2$ Hz, H-4'), 7.19 (d, 1H, $J = 3.6$ Hz, H-3'), 7.38 (t, 1H, $J = 8.0$ Hz, H-7), 7.49 (t, 1H, $J = 8.0$, H-6), 7.60 (brs, 1H, H-5'), 7.89 (d, 1H, $J = 8.0$ Hz, H-8), 8.05 (d, 1H, $J = 8.0$ Hz, H-5); ^{13}C -NMR (100 MHz, CDCl_3): δ 111.33, 112.43, 121.46, 123.01, 125.09, 126.37, 134.17, 144.59, 148.65, 153.64, 157.45.

2-Cyclohexyl-2,3-dihydrobenzothiazole (4i): ^1H -NMR (400 MHz, CDCl_3): δ 0.96-1.32 (m, 5H, cyclohexyl), 1.64-1.93 (m, 6H, cyclohexyl), 4.16 (s, 1H, NH), 5.10 (d, 1H, $J = 6.8$ Hz, H-1), 6.60 (d, 1H, $J = 7.6$ Hz, H-5) 6.70 (t, 1H, $J = 7.6$ Hz, H-7), 6.88 (t, 1H, $J = 8.4$ Hz, H-6)

2-Butyl-2,3-dihydrobenzothiazole (4j): ^1H -NMR (400 MHz, CDCl_3): δ 0.94 (t, 3H, $J = 7.6$ Hz, H-3'), 1.39-1.49 (m, 2H, H-2'), 1.81-1.87 (m, 2H, H-1'), 5.26 (t, 1H, $J = 6.4$ Hz, H-2), 6.62 (d, 1H, $J = 7.6$ Hz, H-5), 6.71 (t, 1H, $J = 7.6$ Hz, H-7), 6.87 (t, 1H, $J = 7.6$ Hz, H-6), 7.03 (d, 1H, $J = 7.6$ Hz, H-8).

Results

The synthesis of benzothiazole (3) and benzothiazoline (4) was investigated *via* Friedel Crafts cyclocondensation of 2-aminothiophenol (1a) with various aldehyde substrates (2). The reaction between 2-aminothiophenol (1a, 1.0 mmol) and benzaldehyde (2a, 1.0 mmol) was selected as a model to evaluate the catalytic activity in aqueous media at room temperature. The results were summarized in Table 1.

Initially, three catalysts, including TCT, DBSA, and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (Senapak *et al.*, 2018) were compared (Table 1, entries 1-3, respectively). Each reaction was conducted in the presence of 10 mol% catalyst at room temperature for 3.0 hours. Among these, TCT provided the highest yield of the desired products 3a and 4a. Consequently, TCT was chosen as the catalyst for further studies. A control experiment was carried out in the absence of catalyst under the same conditions, resulted in an incomplete reaction, affording only trace amounts of product 3a in 7% yield and product 4a in 72% (entry 4). Furthermore, the reaction temperature was increased to 60 °C based on the optimized conditions (entry 1 in parentheses). It was found that the yield of benzothiazole (3a)

remained relatively unchanged at 71%, while product **4a** was not detected, resulting in a decrease in the overall yield of the combined products (**3a** and **4a**). This reduction is likely due to the thermal degradation of product **4a** at the elevated temperature, while product **3a** remained stable under the heating conditions.

Based on the best performing TCT catalyst, the effect of reaction time and water volume was evaluated under the reaction model (entries 5-9). When the reaction time was extended to 6.0 hours with 3.0 mL of water (entry 5), a decrease in product yield was observed, accompanied by the presence of undesirable spots on the TLC. This suggests that prolonged reaction times may lead to product degradation. On the other hand, shortening the reaction time to 1.0 hour (entry 6) also resulted in a decrease in yield, likely due to incomplete reactions, with unreacted starting materials still present on the TLC. When the amount of water was reduced to 1.0 mL (entry 7), a slight decrease in yield was observed. This reduction may have led to a higher concentration of the catalyst, increasing the acidity of the reaction medium, which could promote product degradation. When both the reaction time and water volume were reduced (entries 8 and 9), the product yield remained comparable to the optimal condition (entry 1 vs entry 8), although the overall combined yield was slightly lower. However, reducing the water volume to 1.0 mL and the reaction time to 1.0 hour (entry 9) resulted in significantly lower yields, highlighting the importance of carefully optimizing both time and solvent volume for maximizing product formation.

Subsequently, the effect of catalyst loading was investigated by reducing it from 10 mol% to 5 mol%. As a result, the product yields decreased to 46% for **3a** and 11% for **4a** (entry 10). The highest product yield was achieved with a longer reaction time of 5.0 hours, yielding 80% for **3a** and 11% for **4a** (entry 11). When the volume of water was reduced to 1.0 mL and the reaction time was extended to 8.0 hours, the yield decreased to 31% for **3a** and 49% for **4a** (entry 12). However, product **4a** could convert to product **3a** under oxidation conditions. Therefore, to improve the yield of **3a** from **4a** through oxidation, the use of an oxidant as an oxidant was further investigated. However, only a slight increase in the yield of **3a** was observed (entry 13). Additionally, a reaction carried out at 0°C was studied, but the yield of the product was lower compared to reactions at room temperature (entry 14). This suggests that temperature plays a significant role in the efficiency of the reaction, with lower temperatures potentially hindering the desired product formation. In addition, the catalytic efficiency of TCT was compared with three acid catalysts, including Dowex, acetic acid, and hydrochloric acid (entries 15-17, respectively). The results showed that the TCT catalyst provided a higher product yield compared to all three acid catalysts. This confirms that TCT is more efficient than the other acid catalysts.

Table 1 Optimization^a

entry	catalyst (mol%)	water (mL)	time (h)	yield (%) ^b		total
				3a	4a	
1 ^c	TCT (10)	3.0	3.0	71(71) ^c	28(0) ^c	99(71) ^c
2	DBSA (10)	3.0	3.0	63	4	67
3 ^d	FeCl ₃ ·6H ₂ O (10)	3.0	3.0	38	0	38
4 ^d	-	3.0	3.0	7	72	79
5	TCT (10)	3.0	6.0	46	11	57
6	TCT (10)	3.0	1.0	56	33	89
7	TCT (10)	1.0	3.0	69	18	87
8	TCT (10)	2.0	1.0	73	10	83
9	TCT (10)	1.0	1.0	44	36	80
10	TCT (5)	3.0	3.0	46	11	57
11	TCT (5)	3.0	5.0	80	11	91
12	TCT (5)	1.0	8.0	31	49	80
13 ^e	TCT (5)	3.0	5.0	46	32	78
14 ^f	TCT (5)	3.0	5.0	58	17	75
15	Dowex (5)	3.0	5.0	54	33	87
16	AcOH (5)	3.0	5.0	56	25	81
17	HCl (5)	3.0	5.0	30	42	72

^aThe reactions were conducted with 1.0 mmol of **1a**, 1.0 mmol of **2a** and 5-10 mol% of catalyst in 1.0-3.0 mL of H₂O at room temperature for 1.0-3.0 hours. ^bIsolated yields; ^cSenapak *et al.*, 2018. ^d60 °C. ^eunder oxygen. ^fat 0 °C.

Although water is recognized as a green solvent and was initially chosen as the optimal solvent for this approach, further studies were conducted to confirm the efficiency of the TCT catalyst by comparing reactions in various organic solvents. The investigation included both polar and non-polar organic solvents, which afforded high to excellent product yields (74–94%). The results are summarized in Table 2.

Polar protic solvents such as EtOH, MeOH, and H₂O yielded products in the range of 81–91%. In contrast, polar aprotic solvents such as THF, DMF, and 1,4-dioxane provided higher yields, ranging from 90–94%. These results clearly indicate that polar aprotic solvents gave better outcomes than polar protic solvents, likely due to their higher polarity, which enhances reaction efficiency. Among the tested solvents, 1,4-dioxane gave the highest product yield (94%, entry 6). Therefore, 1,4-dioxane was selected as the optimal organic solvent for this reaction. In contrast, non-polar aprotic solvents such as DCE, MeCN, and toluene produced the product in lower yields (74–81%), though these yields were still considered acceptable. Additionally, the ionic liquid ([bmim][Br]) was tested and provided a high yield (76%, entry 10). This suggests that the TCT catalyst is highly effective in a variety of solvents, demonstrating its versatility and powerful catalytic potential.

Table 2 Optimization with various solvent^a

Nc1ccsc1 (1a) + O=Cc1ccccc1 (2a) $\xrightarrow[\text{solvent, rt, 5.0 h}]{\text{TCT (5 mol\%)}}$ c1ccc(cc1)-c2ccsc2 (3a) $\xrightarrow{\text{oxidation}}$ c1ccc(cc1)-c2cc[nH]s2 (4a)

entry	solvent	yield (%) ^b		total	entry	solvent	yield (%) ^b		total
		3a	4a				3a	4a	
1	EtOH	86	0	86	6	1,4-Dioxane	94	0	94
2	MeOH	81	0	81	7	DCE	77	4	81
3	H ₂ O	80	11	91	8	MeCN	80	0	80
4	THF	90	0	90	9	Toluene	70	4	74
5	DMF	91	0	91	10	[bmim][Br]	76	6	72

^aThe reactions were conducted with 1.0 mmol of **1a**, 1.0 mmol of **2a** and 5 mol% of TCT in 3.0 mL of solvent at room temperature for 5.0 h; ^bIsolated yields.

After establishing the optimized reaction conditions, this study expanded the substrate scope to explore a broader range of potentially interesting products. Ten different aldehydes, including aliphatic aromatic and heteroaromatic aldehydes were investigated. These included benzaldehyde (**2a**), 4-fluorobenzaldehyde (**2b**), 4-nitrobenzaldehyde (**2c**), 4-hydroxybenzaldehyde (**2d**), vanillin (**2e**), 4-methoxybenzaldehyde (**2f**), pyrrole-2-carbaldehyde (**2g**), furan-2-carbaldehyde (**2h**), cyclohexanecarbaldehyde (**2i**), and butanal (**2j**).

The reactions were carried out under two optimized conditions using water and 1,4-dioxane as solvents. Each reaction was performed with 1.0 mmol of 2-aminothiophenol (**1a**) and 1.0 mmol of the aldehyde substrate (**2a-2j**) in the presence of 5 mol% TCT catalyst, in either 3.0 mL of water or 1,4-dioxane. The reactions were conducted at room temperature for 5.0 hours. The product yields obtained under these conditions are summarized in Table 3.

This approach demonstrated versatility with a wide range of aldehydes, including aliphatic, aromatic, and heteroaromatic substrates, providing the corresponding products in good to excellent yields. Benzaldehyde (**2a**) produced the product **3a** in high yield (80%) along with a small amount of **4a** (11%) when water was used as the solvent, while the yield of **3a** increased to an excellent 94% when 1,4-dioxane was employed (entry 1). In the case of aromatic aldehydes bearing nonpolar electron-withdrawing groups such as fluorine (-F), the reaction afforded the product **3b** in a lower yield (44%) with a higher proportion of the intermediate product **4b**. However, using 1,4-dioxane as the solvent still resulted in excellent yield of **3a** (89%), accompanied by only a trace amount of **4a** (9%) (entry 2). The significant presence of **4b** in water system is likely due to its resistance to further oxidative transformation under aqueous conditions. An aromatic aldehyde bearing a polar electron-withdrawing substituent (-NO₂) exhibited poor solubility and tended to solidify during the reaction in the water medium, resulting in lower yields, 60% for **3c** and 16% for **4c**, giving a total yield of 76%. Interestingly, when 1,4-dioxane was used as the solvent, a large amount of the unoxidized intermediate product **4c** remained (64%), while only 25% of the product **3c** was obtained (entry 3), suggesting that the oxidation step was significantly suppressed under these conditions.

Aromatic aldehydes bearing electron-donating substituents yielded only the desired products **3d**, **3e**, and **3f** in high to excellent yields in both water and 1,4-dioxane solvents, 88% and 98% for **3d** (entry 4), 84% and 95% for **3e** (entry 5), and 94% and 96% for **3f** (entry 6), respectively. Heteroaromatic aldehydes, such as pyrrole-2-carbaldehyde (**2g**), afforded low yields of product **3g** (21% in water and 20% in 1,4-dioxane), while the unoxidized intermediate product **4g** was obtained in moderate yields with 51% and 54%, respectively (entry 7). Furan-2-carbaldehyde (**2h**) exhibited a similar trend in water, giving **3h** at 14% and **4h** at 69%. In contrast, the use of 1,4-dioxane significantly improved the yield of **3h** (89%) with only a trace amount of **4h** (9%) (entry 8), indicating

enhanced oxidation efficiency. Unfortunately, aliphatic aldehydes did not successfully produce the desired products **3i** and **3j**. Instead, the unoxidized intermediate products **4i** and **4j** were obtained in low to moderate yields, 20% and 18% for **4i** (entry 9), and 60% and 65% for **4j** in water and 1,4-dioxane, respectively (entry 10).

Table 3 Synthesis of benzothiazoles with various aldehyde^a

entry	structure of the products	solvent	yield (%) ^b		total
			3	4	
1		H ₂ O	80	11	91
		1,4-dioxane	94	0	94
2		H ₂ O	44	54	98
		1,4-dioxane	89	9	98
3		H ₂ O	60	16	76
		1,4-dioxane	25	64	89
4		H ₂ O	88	0	88
		1,4-dioxane	78	0	78
5		H ₂ O	84	0	84
		1,4-dioxane	95	0	95

^aThe reactions were carried out with 1.0 mmol of 2-aminothiophenol (**1a**), 1.0 mmol of aldehyde (**2**) and 5 mol% of TCT in 3.0 mL of solvent at room temperature for 5.0 h, ^bIsolated yields.

Table 3 (continue) Synthesis of benzothiazoles with various aldehyde^a

entry	structure of the products	solvent	yield (%) ^b		total
			3	4	
6		H ₂ O	94	0	94
		1,4-dioxane	96	0	96
7		H ₂ O	21	51	72
		1,4-dioxane	20	54	74
8		H ₂ O	14	69	83
		1,4-dioxane	89	9	98
9		H ₂ O	0	20	20
		1,4-dioxane	0	18	18
10		H ₂ O	0	60	60
		1,4-dioxane	0	65	65

^aThe reactions were carried out with 1.0 mmol of 2-aminothiophenol (**1a**), 1.0 mmol of aldehyde (**2**) and 5 mol% of TCT in 3.0 mL of solvent at room temperature for 5.0 h, ^bIsolated yields.

Discussion

The synthesis of benzothiazole (**3**) and benzothiazoline (**4**) derivatives *via* Friedel Crafts cyclocondensation of 2-aminothiophenol with various aldehydes was systematically investigated to assess the catalytic efficiency of cyanuric chloride (TCT). A model reaction using benzaldehyde (**2a**) and 2-aminothiophenol (**1a**) was employed to optimize the reaction conditions at room temperature as shown the results in Table 1. Various catalysts were studied, including TCT, DBSA and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, affording higher yields of the desired products (Table 1, entries 1-3). In contrast, a control reaction without catalyst produced low yields, confirming the essential role of TCT in facilitating the cyclocondensation (Table 1, entry 4). These findings highlight the suitable catalyst of TCT for this reaction and its efficacy under mild conditions. Temperature played a crucial role in product distribution. Raising the temperature to 60°C resulted in degradation of benzothiazoline (**4a**), while benzothiazole (**3a**) remained stable (Table 1, entry 1 in parentheses). This outcome suggests that **4a** is thermally sensitive and that ambient temperature conditions are optimal for maintaining product stability. Reaction time and water volume were also key variables. Prolonging the reaction time to 6.0 hours resulted in a reduced yield and signs of product decomposition (Table 1, entry 5), while shortening the time to 1.0 hour led to incomplete conversion (Table 1, entry 6). Reducing the water volume to 1.0 mL also slightly lowered yields, likely due to increased acidity in the reaction medium (Table 1, entry 7). Further variations in time and solvent volume (Table 1, entries 8 and 9) emphasized the critical role of condition optimization in ensuring high efficiency. Catalyst loading studies showed that reducing TCT from 10 mol% to 5 mol% resulted in significantly lower yields (Table 1, entry 10). While longer reaction times partly mitigated this effect, excessive extension or reduced water volumes negatively impacted product formation (Table 1, entries 11 and 12). Attempts to improve yields of **3a** by oxidizing intermediate **4a** with external oxidants (oxygen) led to only marginal improvements (Table 1, entry 13), suggesting that *in situ* oxidation under mild conditions is more effective. Lowering the temperature to 0°C further decreased product formation (Table 1, entry 14), reinforcing the importance of room temperature for efficient catalysis. Comparative studies with other acid catalysts, such as Dowex, acetic acid, and hydrochloric acid, confirmed that TCT demonstrated superior catalytic performance (Table 1, entries 15-17).

Although water was initially selected as a green solvent, additional solvent screening offered greater insight into the versatility of TCT (Table 2). Polar protic solvents such as ethanol and methanol gave good yields, while polar aprotic solvents afforded the highest yields. Non-polar solvents yielded moderate results; nevertheless, TCT demonstrated consistent catalytic efficiency throughout a broad range of solvents. Among these, 1,4-dioxane gave

the highest yield of benzothiazole (**3a**) in 94% without forming benzothiazoline (**4a**), therefore, it was selected as the optimal organic solvent for this approach (Table 2, entry 6).

Substrate scope analysis (Table 3) demonstrated that the method is broadly applicable to a wide range of aldehydes. Aromatic aldehydes, particularly those with electron-donating substituents, gave high yields of benzothiazole derivatives. In contrast, aldehydes with electron-withdrawing or heteroaromatic groups often favored the formation of unoxidized benzothiazolines, especially in aqueous media. For instance, 4-nitrobenzaldehyde and pyrrole-2-carbaldehyde favored accumulation of intermediates (**4c**, **4g**). Aliphatic aldehydes failed to produce the benzothiazoles (**3i** and **3j**) and instead only yielded benzothiazolines (**4i** and **4j**), likely due to their lower reactivity and limited in situ oxidation.

Conclusions

In summary, this study demonstrates that cyanuric chloride (TCT) is an effective and efficient catalyst for the synthesis of benzothiazole and benzothiazoline derivatives *via* Friedel-Crafts cyclocondensation of 2-aminothiophenol with a wide range of aldehydes, including aliphatic, aromatic, and heteroaromatic substrates. Reaction optimization was thoroughly explored under various conditions such as reaction time, solvent type, water volume, and catalyst loading. The reactions proceeded smoothly at room temperature in both water and 1,4-dioxane solvents, affording the corresponding products in good to excellent yields (up to 96%). Furthermore, this study highlights the use of a safe, non-toxic catalyst and emphasizes the potential of this method as a green and sustainable approach to organic synthesis.

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