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Cyanide as a powerful catalyst for facile synthesis of benzofused heteroaromatic compounds via aerobic oxidation

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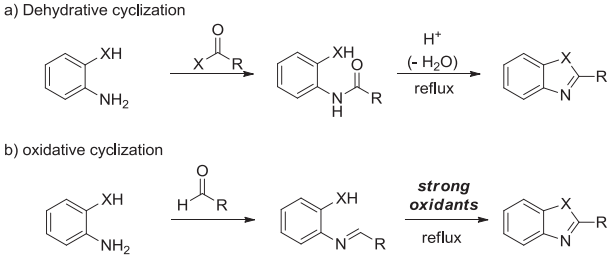
ABSTRACT

Highly efficient synthesis of benzofused heteroaromatic compounds via aerobic oxidation catalyzed by cyanide anion has been developed. The Schiff bases derived from 2-aminophenol and aldehydes provided the corresponding benzoxazoles in high yields in the presence of a catalytic amount of cyanide in an open flask under ambient conditions without the use of any external metal co-oxidants and bases. Furthermore, we have developed a catalytic sequential one-step protocol for the synthesis of benzoxazoles by adding a catalytic amount of NaCN to Schiff bases generated in situ from 2-aminophenol and aldehydes without the isolation of imine intermediates. This one-pot protocol was further extended to the synthesis of benzothiazoles from 2-aminothiophenol and aldehydes. A variety of aldehydes could be applied to this sequential one-pot protocol and the desired benzofused azole products were obtained in high yields.

1. Introduction

Benzofused heteroaromatic compounds, in particular benzofused azoles, are important building blocks in biologically and therapeutically active compounds, natural products, and functional materials.[1] Consequently, a number of methods have been developed for the synthesis of these important building blocks.[2–4] One of the conventional methods for the preparation of the benzofused heteroaromatic compounds involves the condensation of the corresponding aniline derivatives bearing nucleophilic moiety (XH in Scheme 1) at the *ortho*-position with carboxylic acids or their derivatives followed by cyclization reaction in the presence of strong acids at high temperature through dehydration (Scheme 1(a)).[5] Alternatively, these important building blocks are prepared via oxidative cyclization of Schiff bases derived from the corresponding *ortho*-substituted aniline derivatives with aldehydes in the presence of strong oxidants.[6–8] However, this method requires the use of stoichiometric or excess amounts of strong oxidants as compared to the respective Schiff base substrates (Scheme 1(b)).

Recently, aerobic oxidations employing oxygen as the ultimate oxidant have attracted much attention from the synthetic community.[9] In this regard, several examples of the synthesis of benzofused azole compounds via aerobic oxidations have been reported.[10–12] However, most aerobic oxidation protocols developed generally require toxic metal catalysts and/or excess quantities of bases under relatively harsh reaction conditions. Thus, the development of a more efficient method for the synthesis of benzofused heteroaromatic compounds via aerobic oxidation under mild conditions is highly desired.



Scheme 1. Conventional approaches for the synthesis of benzofused heteroazole compounds (X=O, S, and NH).

Recently, we have reported that a nucleophile could act as an efficient catalyst for the synthesis of benzofused heteroaromatic compounds through aerobic oxidation. For example, cyanide efficiently converted Schiff bases derived from *ortho*-aminophenol and aldehydes to the corresponding benzoxazoles in an open flask under ambient conditions without using any other metal salts and bases.[13,14] We have also developed a one-pot protocol for the synthesis of benzoxazoles from *ortho*-aminophenols and aldehydes in the presence of stoichiometric amount of cyanide without the isolation of imine intermediates. However, it was observed that the

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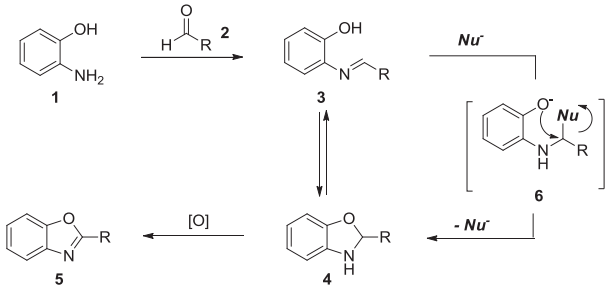
yields from the one-pot protocol were somewhat lower than those from the reactions with the corresponding imines due to benzoin reactions of the aldehydes in the presence of NaCN.[15] In addition, although the cyanide used for this transformation could be removed by a simple aqueous extraction, the need to use a stoichiometric amount of NaCN might lead the synthetic community to be reluctant to use this protocol. In order to overcome the lower yields from the one-pot protocol and stoichiometric use of NaCN, we have developed a more efficient synthetic protocol for the synthesis of benzoxazoles through the sequential addition of a catalytic amount of NaCN to Schiff bases generated in situ from aldehydes and *ortho*-aminophenols.

Herein we would like to report the development of highly efficient cyanide-catalyzed synthesis of benzoxazoles from the corresponding Schiff bases via aerobic oxidation. We also described the improved synthetic protocol for the catalytic one-pot synthesis of benzoxazoles through subsequent addition of a catalytic amount of NaCN to the Schiff bases generated from 2-aminophenols with aldehydes without the isolation of imine intermediates. This sequential one-pot method was further extended to the synthesis of benzothiazoles with 2-aminothiophenol.

2. Results and discussion

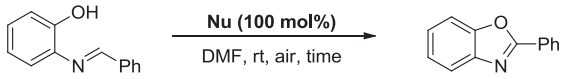
Although several methods for the synthesis of benzoxazoles via aerobic oxidation have been developed,[10] most of the aerobic oxidation methods require the use of metal catalysts and super-stoichiometric amounts of bases under relatively harsh reaction conditions. Thus, we first attempted to develop a method to prepare benzoxazoles from Schiff bases through the aerobic oxidative cyclization using air as a terminal oxidant under mild reaction conditions without any assistance of metal catalysts and/or bases. It is generally accepted that the formation of benzoxazole **5** from Schiff base **3** proceeds in a two-step sequence (Scheme 2).[6] The first step is an equilibrium step between Schiff base **3** and benzoxazoline intermediate **4**. Benzoxazoline **4** undergoes subsequent oxidation to afford benzoxazole **5**. We hypothesized that under aerobic oxidative cyclization of Schiff base **3**,[10] the first equilibrium step might be the rate determining step for the overall process. In this scenario, if the rate of the first step were accelerated, the overall reaction rate for the synthesis of benzoxazole could increase. One way to facilitate the rate of the first step might be addition of a nucleophile. A more reactive nucleophile could readily add to the imine in Schiff base **3** to afford intermediate **6**, which could more easily undergo a ring closing reaction to generate benzoxazoline **4** due to the better leaving ability of the nucleophile. Overall, the nucleophile was expected to decrease the activation energy for the first equilibrium step, which eventually facilitates the formation of benzoxazole **5**.



Scheme 2. Working hypothesis.

In order to test our working hypothesis, we commenced with our studies to find a suitable nucleophile to promote this transformation via aerobic oxidation under ambient conditions (Table 1).

Table 1
Screening of nucleophiles



3a 5a

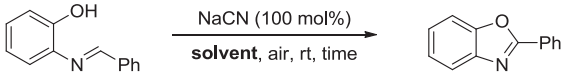
Entry	Nucleophile	Time (h)	Yield (%)[a]
1	—	96	N.R.[b]
2	NaCN	1	92
3	NaSPh	24	N.R.[b]
4	NaOPh	24	N.R.[b]
5	NaOAc	24	N.R.[b]
6	NaO*t*-Bu	24	N.R.[b]
7	DMAP	24	N.R.[b]
8	NEt_3	24	N.R.[b]
9	KCN	1	91
10[c]	NaCN	48	30

[a] Isolated yield.
[b] N.R. means no reaction.
[c] Under argon atmosphere.

To our delight, the addition of a nucleophile significantly facilitated the formation of benzoxazole; with a stoichiometric amount of NaCN the desired product **5a** was obtained in quantitative yield at room temperature in an open flask in 1 h (entry 2), whereas no oxidative cyclization reaction did proceed in the absence of a nucleophile even after 4 days (entry 1). We further examined the possibility of other metal salts and nitrogen-based nucleophiles as catalysts for this transformation (entries 3–8). Rather disappointingly, no nucleophiles other than cyanide could promote this oxidative cyclization reaction. The counter cation of cyanide displayed very little difference in the reactivity and KCN was also turned out to be effective in this transformation (entry 9). In order to confirm that air is the terminal oxidant, the same reaction was carried out under an argon atmosphere (entry 10). Under such conditions, benzoxazole **5a** was initially formed but no further conversion was observed thereafter. We believed that the formation of benzoxazole **5a** at the beginning of the reaction might be due to the oxidative cyclization of Schiff base **3a** with the oxygen dissolved in DMF and the oxidation reaction proceeded until the dissolved oxygen was completely consumed. Upon the complete consumption of the dissolved oxygen, however, no further formation of benzoxazole was observed. These results strongly supported that the air is the terminal oxidant in this transformation.

Next, other reaction parameters were optimized (Table 2). Interestingly, the choice of solvent had a significant effect on the

Table 2
Optimization of reaction conditions



3a 5a

Entry	Solvent	Time (h)	Yield (%)[a]
1	DMF	1	92
2	Dioxane	24	Trace
3	THF	24	Trace
4	EtOH	24	75
5	CH_3CN	24	70
6[b]	DMSO	1	92 (99)[c]
7[b,d]	DMSO	8	93 (99)[c]
8[b,e]	DMSO	48	90 (97)[c]
9[b,f]	DMSO	96	74 (90)[c]

[a] Isolated yield.
[b] DMSO-d_6 was used.
[c] The yields in parentheses were determined by ^{1}H NMR analysis of the crude mixture.
[d] 10 mol % of NaCN was used.
[e] 5 mol % of NaCN was used.
[f] 1 mol % of NaCN was used.

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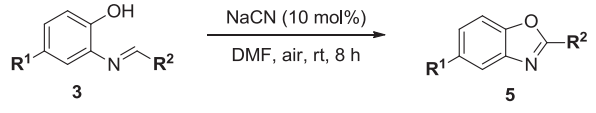
reaction rate (entries 1–6). Etherated solvents provided a trace amount of the product (entries 2 and 3), while several polar solvents gave the desired product **5a** in high to excellent yield (entries 4–6). Among the solvents tested, DMF and DMSO turned out to be the best choice of solvents and the benzoxazole **5a** were obtained in excellent yield in both solvents (entries 1 and 6). Based on our initial hypothesis, this reaction should intrinsically proceed even with a catalytic amount of cyanide. Thus, we explored the possibility for the synthesis of benzoxazole with a catalytic amount of cyanide (entries 6–9). Delightfully, the catalytic amount of cyanide displayed enough reactivity to promote the reaction and the catalyst loading could be lowered as low as 1 mol % without any significant loss of its catalytic efficiency. It should be noted that this transformation is extremely simple and convenient compared to the methods previously developed;[6,10] benzoxazole formation was completed using air as the sole oxidant without the use of metal co-oxidants and bases at room temperature in the presence of a catalytic amount of cyanide and the catalyst loading could be lowered to 1 mol % without any loss of its efficiency.

Under the optimized conditions, the scope of the reaction with respect to Schiff bases **3** derived from various aldehydes was investigated in the presence of 10 mol % of NaCN (Table 3). The electronic properties of aldehydes (R^2 moieties in Schiff bases **3**) had little effect on the formation of benzoxazoles and the desired products were obtained in high yields regardless of the electronic natures of the aryl groups (entries 1–6). However, the steric bulk of aldehydes had a slightly deleterious effect on the reactivity for this transformation. 20 mol % of NaCN should be used for Schiff bases from sterically congested aldehydes to get high yields (entries 7, 8, and 11). It should be noted that several functional groups, such as ester, ether, and hydroxy groups, were well-tolerated under the reaction conditions. The electronic properties of *ortho*-aminophenol ring (R^1 in Schiff bases **3**) also had minimal effect on the formation of benzoxazoles (entries 12 and 13). Imines derived from *ortho*-aminophenols bearing either electron donating or electron withdrawing substituents provided the desired products in high yields. In order to demonstrate practicality of this method in the synthesis of benzoxazoles, we carried out this transformation on a gram scale. Delightfully, the desired benzoxazole **5a** was obtained in a 10 mmol scale without any loss of its efficiency (entry 14).

Table 3
Substrate scope



3 5

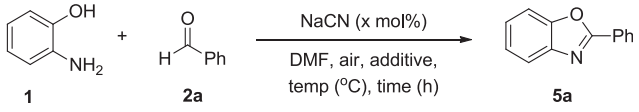
Entry	Benzoxazoles **5**			Yield (%)[a]
	5	R^1	R^2	
1	**5a**	H	Ph	93 (92)[b]
2	**5b**	H	4-(MeO_2C)C_6H_4	76
3	**5c**	H	4-ClC_6H_4	86
4	**5d**	H	4-(*t*-Bu)C_6H_4	78
5	**5e**	H	4-(Me)C_6H_4	81
6	**5f**	H	4-(MeO)C_6H_4	80
7[c]	**5g**	H	2-(Me)C_6H_4	80
8[c]	**5h**	H	2-(MeO)C_6H_4	82
9	**5i**	H	2-(HO)C_6H_4	82
10	**5j**	H	2-Naphthyl	81
11[c]	**5k**	H	1-Naphthyl	81
12	**5l**	Me	Ph	80
13	**5m**	Cl	Ph	84
14[d]	**5a**	H	Ph	85

[a] Isolated yield.
[b] 100 mol % of NaCN was used.
[c] 20 mol % of NaCN was used.
[d] The reaction was carried out in 10 mmol scale.

One of the drawbacks of the synthesis of benzoxazoles from Schiff bases via oxidative cyclization is that the imines have to be prepared prior to the oxidative cyclization reaction.[16] We envisioned that as long as cyanide did not interfere in the imine formation reaction (Scheme 2), benzoxazoles could be directly prepared from *ortho*-aminophenol and aldehydes without the isolation of imines.

To test this idea, 2-aminophenol **1**, benzaldehyde **2a**, and 10 mol % of NaCN were dissolved in DMF and the reaction mixture was monitored at room temperature in an open flask. However, under such conditions only a trace amount of benzoxazole **5a** was observed even after a long reaction time (Table 4, entry 1). Since the low yield was presumably attributed to the inefficient formation of imine **3a**,[17] the same reaction was carried out at 60 °C in the presence of molecular sieves with a stoichiometric amount of NaCN. Delightfully, the desired benzoxazole **5a** was obtained in 78% yield in 4 h (entry 2). The catalytic amount of NaCN could also afford the desired benzoxazole **5a** in comparable yield with the stoichiometric reaction albeit a longer reaction time (entry 3 vs entry 2).

Table 4
Optimization of one-pot reaction

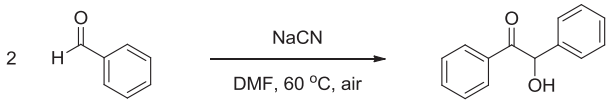


1 2a 5a

Entry	Additive	NaCN (x mol %)	Temp (°C)	Time (h)	Yield (%)[a]
1	—	10	rt	24	Trace
2	4 Å MS	100	60	4	78
3	4 Å MS	10	60	24	74
4[b]	4 Å MS	100	rt	1	85
5[b]	4 Å MS	10	rt	12	87

[a] Isolated yield.
[b] NaCN was added to the imine generated in situ from **1** and **2a** at 60 °C for 2 h.

However, it was observed that the yields from the one-pot protocols with a catalytic and/or stoichiometric amount of NaCN were lower than those with the corresponding imine **3a** (Table 4 entries 2 and 3 vs Table 3, entry 1). In addition, although a 1:1 ratio of 2-aminophenol and benzaldehyde was used, 2-aminophenol remained even after the complete consumption of benzaldehyde. We suspected that the slight lower yields from the one-pot protocol might be due to the interference of cyanide in the imine formation step. Indeed, cyanide promoted the benzoin reaction with aldehyde **3a** and a measurable amount of the benzoin product of aldehyde **2a**[15] was detected in the reaction mixture (Scheme 3).



2a

Scheme 3. Formation of benzoin product catalyzed NaCN.

In order to overcome the lower yield from the one-pot protocol, we attempted to subsequently add NaCN to imine **3a** generated in situ from 2-aminophenol **1** and benzaldehyde **2a**. Fortunately, this sequential one-pot protocol provided benzoxazole **5a** in higher yield with both a stoichiometric and a catalytic amount of NaCN (entries 4 and 5) than the simple one-pot protocol (entries 2 and 3) and thus we decided to use this sequential one-pot method for further investigation.

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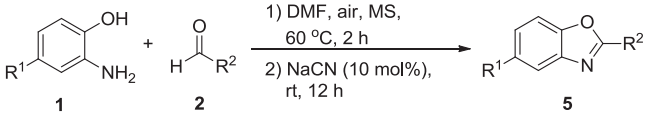
Under these conditions, we examined the substrate scope for the sequential one-pot protocol for the synthesis of benzoxazoles from aldehydes and *ortho*-aminophenols with 10 mol % of NaCN (Table 5). Imines were easily prepared from aldehydes and *ortho*-aminophenols in the presence of molecular sieves at 60 °C and subsequent addition of a catalytic amount of NaCN afforded the desired products in high yields at room temperature. The electronic properties of aldehydes and/or *ortho*-aminophenols had little effect on the formation of benzoxazoles (entries 1–5). Heteroaromatic aldehydes were also employed in this method and the desired benzoxazoles were obtained in high yields (entries 6 and 7). We could extend the method to more challenging aliphatic substrates. It is generally known that the aliphatic substrates are challenging in the oxidative cyclization method not only because of instability of imines of aliphatic aldehydes, but also unwanted side reactions, such as intermolecular aldol reaction.[10d] When a catalytic amount of NaCN was used for aliphatic substrates, the desired benzoxazoles was obtained in low yield along with many side-products. However, when a simple one-pot protocol was used for these aliphatic substrates with a stoichiometric amount of NaCN, aliphatic aldehydes afforded the desired 2-alkyl benzoxazoles in high yields (entries 8–10). It should be noted that aliphatic aldehydes even bearing acidic α-protons were also applied to this one-pot protocol without any sacrifice of efficiency. In addition, the sequential one-pot protocol for the synthesis of benzoxazole **5a** could be performed on a gram scale, and benzoxazole **5a** was obtained in a similar yield to that obtained from the reaction from the corresponding imine **3a** (entry 11).

Table 5
Substrate scope of sequential one-pot protocol for synthesis of benzoxazoles **5**

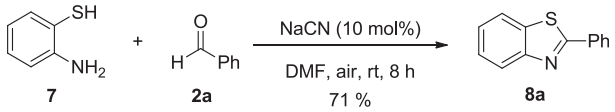


1 2 5

Entry	Benzoxazoles **5**			Yield (%)[a]
	5	R^1	R^2	
1	**5a**	H	Ph	87
2	**5c**	H	4-ClC_6H_4	88
3	**5e**	H	4-MeC_6H_4	95
4	**5l**	Me	Ph	82
5	**5m**	Cl	Ph	83
6	**5n**	H	2-Furyl	90
7	**5o**	H	2-Thienyl	88
8[b]	**5p**	H	*tert*-Butyl	81
9[b]	**5q**	H	*c*-Hexyl	80
10[b]	**5r**	H	*n*-Hexyl	76
11[c]	**5a**	H	Ph	85

[a] Isolated yield.
[b] Reaction was carried out through a simple one-pot protocol with a stoichiometric amount of NaCN.
[c] The reaction was carried out in 10 mmol scale.

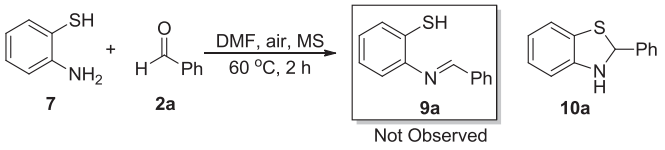
After successfully developing the cyanide-catalyzed one-pot protocol for the synthesis of benzoxazoles, we attempted to extend this aerobic oxidative protocol to the synthesis of benzothiazole **8** with 2-aminothiophenol **7**.[11] Initially, we expected that the higher nucleophilicity of the sulfur in 2-aminothiophenol **7** compared to that of the oxygen in 2-aminophenol **1** might enable us to perform the synthesis of benzothiazoles at a lower temperature than the benzoxazole synthesis. We also expected that benzoin reactions of aldehydes might be prevented or proceed at negligible rate at a lower reaction temperature. With these expectations in mind, we attempted to perform the synthesis of benzothiazole **8a** from 2-aminothiophenol **7** and benzaldehyde **2a** at room temperature by adding benzaldehyde, 2-aminothiophenol, molecular sieves, and 10 mol % of NaCN all at once in DMF. To our delight, benzothiazole **8a** was obtained in 71% yield in an open flask at room temperature (Scheme 4).



7 2a 8a

Scheme 4. One-pot synthesis of benzothiazole **8a**.

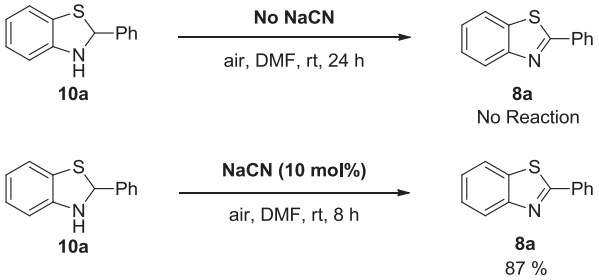
However, we encountered two difficulties in the synthesis of benzothiazole **8a**. First, the yield of **8a** was varied from 40 to 70%. Second, contrary to our initial expectation, the benzoin reaction still took place under such conditions. Thus, we decided to prepare benzothiazole **8a** by the addition of NaCN to imine **9a** generated in situ from benzaldehyde **2a** and 2-aminothiophenol **7**. When benzaldehyde **2a** and 2-aminothiophenol **7** were stirred at 60 °C in the presence of molecular sieves, the corresponding benzothiazoline **10a**, rather than the imine **9a**, was isolated in quantitative yield (Scheme 5).[18]



7 2a 9a 10a

Scheme 5. Preparation of benzothiazoline **10a**.

In our initial hypothesis (Scheme 2), we anticipated that NaCN might catalyze this reaction by facilitating conversion of imine **3** to benzoxazoline **4** rather than the oxidation step. Thus, we were not sure whether NaCN could facilitate the conversion of benzothiazoline **10a** into the corresponding benzothiazole **8a**. Rather surprisingly, NaCN significantly facilitated the formation of benzo thiazole **8a** from benzothiazoline **10a** (Scheme 6).[19] Addition of 10 mol % of NaCN to benzothiazoline **10a** afforded the corresponding benzothiazole **8a** in 87% yield at room temperature in 12 h, whereas benzothiazoline **10a** did not undergo any oxidation in the absence of NaCN even after 24 h.



10a 8a 10a 8a

Scheme 6. Cyanide-catalyzed conversion of benzothiazoline **10a** to benzothiazole **8a**.

We have further developed a sequential one-pot synthesis of benzothiazole **8a** through the addition of a catalytic amount of NaCN to the benzothiazoline **10a** generated in situ from aldehyde **2a** and 2-aminothiophenol **7** without its isolation (Scheme 7). Subsequent addition of NaCN (10 mol %) to the above benzothiazoline **10a** solution afforded benzothiazole **8a** in 85%.

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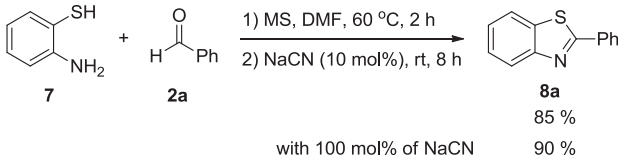
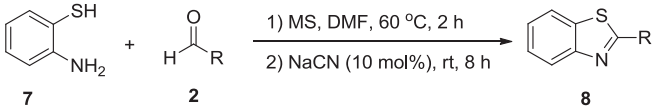


Scheme 7. Sequential one-pot synthesis of benzothiazole **8a**.

With these conditions in hand, we investigated the generality and limitation of this protocol for the synthesis of benzothiazoles **8** (Table 6). Various aldehydes could be applied to this protocol and the desired benzothiazoles **8** were obtained in high yields. The electronic and steric properties of the aromatic rings in aldehydes had little effect on the formation of benzothiazoles and the corresponding benzothiazoles were obtained in high yields regardless of the stereoelectronic properties of the aromatic systems (entries 1–8). Heteroaromatic aldehydes could be also employed in the sequential one-pot protocol, and the desired benzothiazoles were obtained in good to high yields (entries 9–10). This method was further extended to aliphatic aldehydes and the corresponding benzothiazoles were obtained in synthetically useful yields (entries 11–13). Similar to benzoxazoles from aliphatic aldehydes, a simple one-pot protocol should be used in the presence of a stoichiometric amount of NaCN for these aliphatic substrates to avoid unwanted side-reactions. Notably, a gram scale synthesis of benzothiazole **8a** with this sequential one-pot protocol was possible without loss of its efficiency (entry 14).

Table 6
Substrate scope of sequential one-pot protocol of synthesis of benzothiazoles **8**

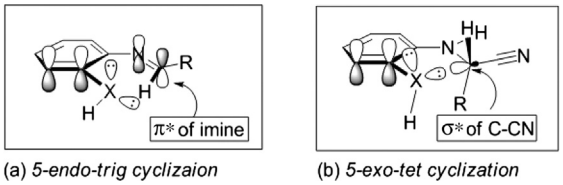


Entry	Benzothiazoles **8**		Yield (%)[a]
	8	R	
1	**8a**	Ph	85 (90)[b]
2	**8b**	4-MeOC$_6$H$_4$	80
3	**8c**	4-MeC$_6$H$_4$	76
4	**8d**	4-ClC$_6$H$_4$	91
5	**8e**	4-MeO$_2$CC$_6$H$_4$	95
6	**8f**	2-MeC$_6$H$_4$	84
7	**8g**	2-MeOC$_6$H$_4$	87
8	**8h**	2-Naphthyl	79
9	**8i**	2-Furyl	80
10	**8j**	2-Thienyl	58
11[c]	**8k**	*tert*-Butyl	52
12[c]	**8l**	*c*-Hexyl	62
13[c]	**8m**	*n*-Hexyl	57
14[d]	**8a**	Ph	85

[a] Isolated yield.
[b] 100 mol % of NaCN was used.
[c] Reaction was carried out through a simple one-pot protocol with a stoichiometric amount of NaCN.
[d] The reaction was carried out in 10 mmol scale.

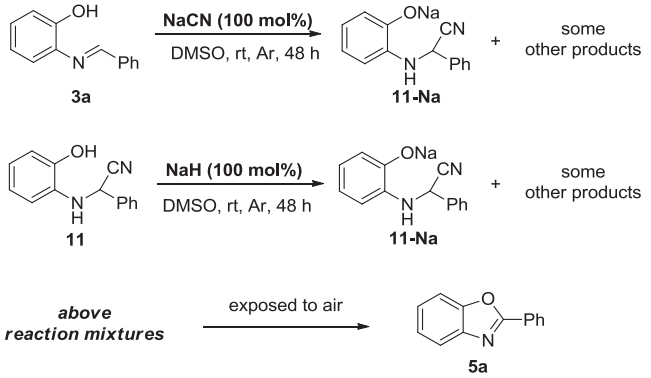
With these results in hand, we would like to gain information to elucidate a plausible reaction mechanism for the synthesis of benzoxazoles **5** and benzothiazoles **8** via aerobic oxidation. In particular, we attempted to understand the role of cyanide for these transformations.

First, we tested our initial working hypothesis in which cyanide might act as a catalyst for the aerobic oxidative cyclization of Schiff base **3** through the facile conversion of imine **3** to the corresponding benzoxazoline **4**. In the absence of cyanide, the lone pair on the oxygen atom in **3a** could not attack the carbon on the imine presumably because such a 5-*endo-trig* cyclization is not allowed by Baldwin's rule (Scheme 8(a)).[20] However, once cyanide was added to the imine, the lone pair on the oxygen atom in intermediate **6** could be properly oriented to the σ* of C–CN bond, and the cyclization reaction more readily take place via an allowed 5-*exo-tet* cyclization to generate intermediate **4** (Scheme 8(b)).



Scheme 8. Possible orbital interaction.

To test this idea we carried out some reactions for the synthesis of benzoxazole under argon atmosphere (Scheme 9). On addition of NaCN to imine **3** under argon atmosphere, the imine immediately disappeared and a Strecker product **11**-**Na** was obtained as the major product along with some products and no further transformation was observed even after a long reaction time under such conditions. In addition, when Strecker product **11** prepared independently[21] was treated with NaH, the similar result was obtained. When both reaction mixtures were exposed to air, the aerobic oxidation rapidly took place to afford the corresponding benzoxazoles.



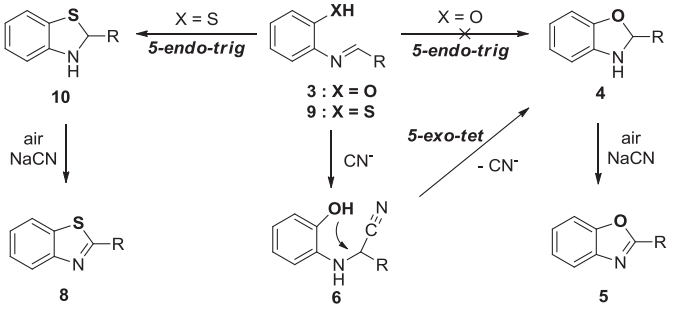
Scheme 9. Reaction of imine **3a** with NaCN under argon atmosphere.

At that moment, however, we were not sure whether or not cyanide might be involved in the aerobic oxidation step. Unlike our initial working hypothesis, cyanide turned out to be involved in the aerobic oxidation in the benzothiazole synthesis. Thus, we expected that cyanide would play a similar role in aerobic oxidation step in the benzoxazole synthesis and be an active catalyst for the aerobic oxidation in the benzoxazole synthesis.

On the other hand, in the benzothiazole synthesis, the higher nucleophilicity and larger size of sulfur in compound **7** compared with oxygen in **1** readily undergoes 5-*endo-trig* cyclization, which allowed us to isolate benzothiazoline rather than the corresponding imines. Subsequent aerobic oxidation in the presence of cyanide afforded the benzothiazole under mild reaction conditions. This increase in the reaction rate for the aerobic oxidation of benzofused azolines to benzofused azoles is presumably due to increase in the concentration of oxygen in DMF with NaCN and/or the change in oxidation potential in DMF via activation of oxygen with NaCN[11a,19].

Considering these results, we proposed possible reaction mechanism for the synthesis of benzoxazole **5** and benzothiazole **8**

via aerobic oxidation (Scheme 10). Similar to our initial working hypothesis, anilines **1** and **7** initially form imines **3** and **9** with aldehydes. For benzoxazole synthesis, the lower nucleophilicity and smaller size of oxygen could not allow imine **3** to undergo cyclization reaction via 5-*endo-trig* cyclization without any assistance of cyanide. However, the addition of cyanide to the imine **3** furnishes intermediate **6**, which could undergo ring closure through 5-*exo-tet* cyclization reaction to yield benzoxazoline **4**. Subsequent aerobic oxidation catalyzed by cyanide generates the desired benzoxazole **3**. On the other hand, for the benzothiazole synthesis, the higher nucleophilicity and larger size of sulfur in imine **9** than the counterpart oxygen in imine **3** make 5-*endo-trig* cyclization possible to afford benzothiazoline **10** even in the absence of cyanide. Subsequent cyanide-catalyzed aerobic oxidation of **10** yields the corresponding benzothioazole **8**.



Scheme 10. Proposed reaction mechanism for the synthesis of benzoxazoles **5** and benzothiazole **8**.

3. Conclusion

We have developed a highly efficient cyanide-catalyzed aerobic oxidative cyclization protocol of Schiff bases for the synthesis of benzoxazoles using air as the terminal oxidant at room temperature. We have also developed the catalytic sequential one-pot protocol for the synthesis of benzoxazoles by the addition of NaCN to imines generated in situ from aldehydes and 2-aminophenol. A broad range of substrates including problematic aliphatic substrates were successfully applied to this catalytic system and the desired products were obtained in high to excellent yields. Moreover, the sequential one-pot reaction was successfully applied to the preparation of benzothiazoles with 2-aminothiophenol. Although several aerobic oxidative cyclization reactions have been developed recently, it is noteworthy to mention that the catalytic systems developed herein are remarkably simple, convenient, and efficient compared to the previous methods reported. Broad substrate scope and easy scale-up for these syntheses might be advantages for this protocol. Further development of synthetic methods for biologically important heteroaromatic compounds via aerobic oxidation is currently underway in our laboratory.

4. Experimental section

4.1. General methods

All reactions were carried out in oven- or flame-dried glassware under air atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using Merck pre-coated silica gel glass plates (0.25 mm) with F_{254} indicator. Visualization was accomplished by UV light (254 nm), with combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (230–400 mesh) supplied by MERCK. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted. ^{1}H NMR spectra were recorded on Varian Gemini 300 (300 MHz) and ^{13}C NMR spectra were recorded on Varian Gemini 400 (100 MHz). Tetramethylsilane and $CDCl_3$ were used as internal standards for ^{1}H NMR (δ: 0.0 ppm) and ^{13}C NMR (δ: 77.16 ppm). The proton spectra were reported as follows δ (position of proton, multiplicity, coupling constant *J*, number of protons) and the carbon spectra were reported only δ (position of carbon). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (heptet), m (multiplet), and br (broad). Commercial grade reagents and solvents were used without further purification. Liquid aldehydes were freshly distilled under an atmosphere of dry argon, and solid aldehydes were purified by flash chromatography on silica gel.

4.2. General procedures for preparation of imines 3

2-Aminophenol **1** (10. mmol; 1.0 equiv) and aldehyde **2** (10. mmol; 1.0 equiv) were dissolved in EtOH (80 mL). Then, the reaction mixture was stirred at 80 °C for 4 h under an argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was recrystallized with EtOH. The solid was collected by filtration and washed with cooled EtOH to give a corresponding imine **3**.

*4.2.1. N-Benzylidene-2-hydroxyaniline (**3a**).*[22] Yield: 1.2 g (61%). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.71 (s, 1H), 7.91–7.95 (m, 2H), 7.49–7.51 (m, 3H), 7.31 (d, *J*=7.97 Hz, 1H), 7.21 (t, *J*=8.24 Hz, 1H), 7.02 (d, *J*=8.24 Hz, 1H), 6.90 (t, *J*=7.43 Hz, 1H).

*4.2.2. Methyl 4-(((2-hydroxyphenyl)imino)methyl)benzoate (**3b**).*[23] Yield: 1.6 g (63%). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.67 (s, 1H), 7.82 (d, *J*=7.97 Hz, 2H), 7.30 (d, *J*=7.69 Hz, 3H), 7.19 (t, *J*=7.69 Hz, 1H), 7.01 (d, *J*=7.97 Hz, 1H), 7.02 (t, *J*=7.97 Hz, 1H).

*4.2.3. N-4-Chlorobenzylidene-2-hydroxyaniline (**3c**).*[22] Yield: 1.6 g (69%). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.67 (s, 1H), 7.86 (d, *J*=8.52 Hz, 2H), 7.47 (d, *J*=8.52 Hz, 2H), 7.30 (d, *J*=7.97 Hz, 1H), 7.20 (d, *J*=9.34 Hz, 1H), 7.02 (d, *J*=8.24 Hz, 1H), 6.91 (d, *J*=7.97 Hz, 1H).

*4.2.4. N-4-tert-Butylbenzylidene-2-hydroxyaniline (**3d**).*[24] Yield: 1.4 g (55%). Reddish brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.68 (s, 1H), 7.86 (d, *J*=8.52 Hz, 2H), 7.47 (d, *J*=8.52 Hz, 2H), 7.30 (d, *J*=7.97 Hz, 1H), 7.20 (d, *J*=9.34 Hz, 1H), 7.02 (d, *J*=8.24 Hz, 1H), 6.91 (d, *J*=7.97 Hz, 1H).

*4.2.5. N-4-Methylbenzylidene-2-hydroxyaniline (**3e**).*[22] Yield: 1.4 g (66%). Dark yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.71 (s, 1H), 7.86 (d, *J*=8.52 Hz, 2H), 7.51 (d, *J*=8.52 Hz, 2H), 7.30 (d, *J*=7.97 Hz, 1H), 7.19 (t, *J*=8.52 Hz, 1H), 7.01 (d, *J*=7.97 Hz, 1H), 6.91 (t, *J*=7.69 Hz, 1H).

*4.2.6. N-4-Methoxybenzylidene-2-hydroxyaniline (**3f**).*[22] Yield: 1.4 g (62%). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.63 (s, 1H), 7.88 (d, *J*=8.79 Hz, 2H), 7.28 (d, 1H), 7.18 (t, *J*=7.69 Hz, 1H), 7.01 (d, *J*=7.97 Hz, 3H), 6.90 (t, *J*=7.69 Hz, 1H), 3.89 (s, 3H).

*4.2.7. N-2-Methylbenzylidene-2-hydroxyaniline (**3g**).*[22] Yield: 1.3 g (62%). Dark brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 9.01 (s, 1H), 8.08 (d, *J*=7.42 1H), 7.18–7.41 (m, 4H), 7.02 (d, *J*=7.97 Hz, 1H), 6.92 (t, *J*=7.42 Hz, 1H), 2.63 (s, 3H).

*4.2.8. N-2-Methoxybenzylidene-2-hydroxyaniline (**3h**).*[25] Yield: 1.5 g (66%). Light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 9.19 (s,

1H), 8.16 (d, *J*=7.69, 1H), 7.46 (t, *J*=7.99 Hz, 1H), 7.33 (d, *J*=7.99 Hz, 1H), 7.18 (t, *J*=7.99 Hz, 1H), 7.06 (t, *J*=7.69 Hz, 1H), 6.99 (t, *J*=7.69 Hz, 2H), 6.90 (t, *J*=7.99 Hz, 1H), 3.93 (s, 3H).

*4.2.9. N-2-Hydroxybenzylidene-2-hydroxyaniline (**3i**).*[26] Yield: 1.5 g (70%). Red solid. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.95 (s, 1H), 7.59 (d, *J*=7.69 Hz, 1H), 7.33–7.40 (m, 2H), 7.11 (t, *J*=7.69 Hz, 1H), 6.93 (t, *J*=7.69 Hz, 3H), 6.86 (t, *J*=7.69 Hz, 1H).

*4.2.10. 2-((Naphthalen-2-ylmethylene)amino)phenol (**3j**).*[22] Yield: 1.7 g (69%). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.87 (s, 1H), 8.18–8.22 (m, 2H), 7.89–7.97 (m, 3H), 7.57 (t, *J*=3.85 Hz, 3H), 7.34–7.39 (m, 1H), 7.21 (d, *J*=7.69 Hz, 1H), 7.05 (d, *J*=8.24 Hz, 1H), 6.94 (t, *J*=7.69 Hz, 1H).

*4.2.11. 2-((Naphthalen-1-ylmethylene)amino)phenol (**3k**).*[22] Yield: 1.6 g (65%). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 9.40 (s, 1H), 8.88 (d, *J*=8.52, 1H), 8.20 (d, *J*=7.14, 1H), 8.01 (d, *J*=8.24 Hz, 1H), 7.95 (d, *J*=7.97 Hz, 1H), 7.56–7.58 (m, 3H), 7.39 (d, *J*=7.97 Hz, 1H), 7.23 (d, *J*=7.69 Hz, 1H), 7.06 (d, *J*=7.97 Hz, 1H), 6.97 (t, *J*=7.69 Hz, 1H).

*4.2.12. N-Benzylidene-2-hydroxy-5-methylaniline (**3l**).*[22] Yield: 1.5 g (71%). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.69 (s, 1H), 7.91–7.95 (m, 2H), 7.49–7.51 (m, 3H), 7.13 (s, 1H), 7.02 (d, *J*=7.97 Hz, 1H), 6.91 (d, *J*=8.24 Hz, 1H), 2.32 (s, 3H).

*4.2.13. N-Benzylidene-2-hydroxy-5-chloroaniline (**3m**).*[26] Yield: 1.6 g (69%). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.67 (s, 1H), 7.91–7.95 (m, 2H), 7.49–7.54 (m, 3H), 7.30 (d, *J*=2.47 Hz, 1H), 7.16 (dd, *J*=8.52, 2.47 Hz, 1H), 7.95 (d, *J*=8.52 Hz, 1H).

4.3. General procedures for synthesis of benzoxazoles 5 from imines 3 (Table 3)

An imine **3** (0.50 mmol: 1.0 equiv) and NaCN (2.5 mg; 0.050 mmol; 10 mol %) were dissolved in DMF (2.0 mL). The reaction mixture was stirred at room temperature in an open flask and monitored by TLC. On the complete consumption of the imine, the reaction mixture was quenched with H_2O, and extracted with Et_2O. The organic layer was collected, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica.

*4.3.1. 2-Phenylbenzoxazole (**5a**).*[6g] Yield: 91 mg (93%), 90 mg (92%, 100 mol % NaCN). R_f=0.6 (EtOAc/hexanes=1:7). White solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.26–8.28 (m, 2H), 7.77–7.80 (m, 1H), 7.58–7.61 (m, 1H), 7.53–7.57 (m, 3H), 7.35–7.38 (m, 2H).

*4.3.2. 2-(4-Acetylphenyl)-benzoxazole (**5b**).*[4b] Yield: 96 mg (76%). R_f=0.3 (EtOAc/hexanes=1:7). White solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.34 (d, *J*=8.24 Hz, 2H), 8.21 (d, *J*=8.52 Hz, 2H) 7.80–7.83 (m, 1H), 7.60–7.63 (m, 1H), 7.38–7.42 (m, 2H), 3.97 (s, 3H).

*4.3.3. 2-(4-Chlorophenyl)-benzoxazole (**5c**).*[6g] Yield: 87 mg (76%). R_f=0.6 (EtOAc/hexanes=1:10). Light red solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.20 (d, *J*=8.24 Hz, 2H), 7.76–7.79 (m, 1H), 7.57–7.61 (m, 1H), 7.51 (d, *J*=8.79 Hz, 2H) 7.36–7.39 (m, 2H).

*4.3.4. 2-(4-tert-Butylphenyl)-benzoxazole (**5d**).*[2g] Yield: 99 mg (78%). R_f=0.7 (EtOAc/hexanes=1:10). Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.19 (d, *J*=8.52 Hz, 2H), 7.75–7.78 (m, 1H), 7.58–7.60 (m, 1H), 7.55 (d, *J*=8.52 Hz, 2H), 7.33–7.36 (m, 2H), 1.39 (s, 9H).

*4.3.5. 2-(4-Methylphenyl)-benzoxazole (**5e**).*[6g] Yield: 85 mg (81%). R_f=0.6 (EtOAc/hexanes=1:7). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.15 (d, *J*=7.97 Hz, 2H), 7.75–7.78 (m, 1H), 7.56–7.59 (m, 1H), 7.32–7.38 (m, 4H), 2.45 (s, 3H).

*4.3.6. 2-(4-Methoxyphenyl)-benzoxazole (**5f**).*[6g] Yield: 90 mg (80%). R_f=0.4 (EtOAc/hexanes=1:7). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.21 (d, *J*=8.79 Hz, 2H), 8.21 (d, *J*=8.52 Hz, 1H) 7.71–7.76 (m, 1H), 7.53–7.58 (t, *J*=4.12, 2H), 7.04 (d, *J*=8.79 Hz, 2H), 3.90 (s, 3H).

*4.3.7. 2-(2-Methylphenyl)-benzoxazole (**5g**).*[6g] Yield: 84 mg (80%). R_f=0.6 (EtOAc/hexanes=1:7). White solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.18 (d, *J*=7.14 Hz, 1H), 7.80–7.83 (m, 1H) 7.58–7.61 (m, 1H), 7.35–7.42 (m, 5H), 2.82 (s, 3H).

*4.3.8. 2-(2-Methoxyphenyl)-benzoxazole (**5h**).*[3b] Yield: 92 mg (82%). R_f=0.4 (EtOAc/hexanes=1:7). Light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.14 (d, *J*=7.69 Hz, 1H), 7.80–7.84 (m, 1H), 7.58–7.61 (m, 1H), 7.51 (t, *J*=7.69 Hz, 1H), 7.33–7.36 (m, 2H), 7.11 (t, *J*=7.97 Hz, 2H), 4.03 (s, 3H).

*4.3.9. 2-(2-Hydroxyphenyl)-benzoxazole (**5i**).*[5h] Yield: 87 mg (82%). R_f=0.5 (EtOAc/hexanes=1:5). White solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.04 (dd, *J*=7.97, 1.37 Hz, 1H), 7.73–7.76 (m, 1H), 7.61–7.64 (m, 1H), 7.45 (td, *J*=8.52, 1.65 Hz, 1H), 7.38–7.41 (m, 2H), 7.13 (d, *J*=8.24 Hz, 1H), 7.02 (t, *J*=7.42 Hz, 1H).

*4.3.10. 2-(2-Naphthyl)-benzoxazole (**5j**).*[4b] Yield: 99 mg (81%). R_f=0.6 (EtOAc/hexanes=1:10). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.80 (s, 1H), 8.33 (d, *J*=8.52 Hz, 1H) 7.98–8.00 (m, 2H), 7.89–7.92 (m, 1H), 7.81–7.84 (m, 1H), 7.57–7.65 (m, 3H), 7.37–7.40 (m, 2H).

*4.3.11. 2-(1-Naphthyl)-benzoxazole (**5k**).*[6g] Yield: 1.0×10^2 mg (81%). R_f=0.6 (EtOAc/hexanes=1:10). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 9.48 (d, *J*=8.79 Hz, 1H), 8.44 (d, *J*=7.42 Hz, 1H), 8.05 (d, *J*=8.24 Hz, 1H), 7.95 (d, *J*=8.24 Hz, 1H), 7.88–7.91 (m, 1H), 7.58–7.75 (m, 4H), 7.39–7.43 (m, 2H).

*4.3.12. 5-Methyl-2-phenylbenzoxazole (**5l**).*[6g] Yield: 84 mg (80%). R_f=0.6 (EtOAc/hexanes=1:7). Light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.23–8.26 (m, 2H), 7.51–7.56 (m, 4H), 7.46 (d, *J*=8.24 Hz, 1H), 7.16 (d, *J*=8.24 Hz, 1H), 2.49 (s, 3H).

*4.3.13. 5-Chloro-2-phenylbenzoxazole (**5m**).*[6g] Yield: 96 mg (84%). R_f=0.6 (EtOAc/hexanes=1:7). White solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.23–8.26 (m, 2H), 7.75 (d, *J*=1.65 Hz, 1H), 7.50–7.56 (m, 4H), 7.33 (dd, *J*=8.52, 1.92 Hz, 1H).

4.4. General procedures for synthesis of benzoxazoles 5 via catalytic sequential one-pot protocol (Table 5)

2-Aminophenol **1** (21.8 mg; 0.20 mmol; 1.0 equiv) and aldehyde **2** (0.20 mmol; 1.0 equiv), and molecular sieve (10 mg) were dissolved in DMF (1.0 mL). The reaction mixture was stirred in an open flask at 60 °C. On complete formation of the corresponding imine, the mixture was cooled to room temperature and NaCN (1.0 mg; 0.020 mmol; 10 mol %) was added to the above reaction mixture and the reaction mixture was monitored by TLC. After complete consumption of the corresponding imine, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica to give the corresponding benzoxazole product **5**.

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*4.4.1. 2-Phenylbenzoxazole (**5a**).*[6g] Yield: 33 mg (85%). White solid. ^{1}H NMR spectrum was in good agreement with those of **5a** obtained via the oxidative cyclization of imine **3a**.

*4.4.2. 2-(4-Chlorophenyl)-benzoxazole (**5c**).*[6g] Yield: 40 mg (86%). Light red solid. ^{1}H NMR spectrum was in good agreement with those of **5c** obtained via the oxidative cyclization of imine **3c**.

*4.4.3. 2-(4-Methylphenyl)-benzoxazole (**5e**).*[6g] Yield: 37 mg (89%). Yellow solid. ^{1}H NMR spectrum was in good agreement with those of **5e** obtained via the oxidative cyclization of imine **3e**.

*4.4.4. 5-Methyl-2-phenylbenzoxazole (**5l**).*[6g] Yield: 38 mg (90%). Light yellow solid. ^{1}H NMR spectrum was in good agreement with those of **5l** obtained via the oxidative cyclization of imine **3l**.

*4.4.5. 5-Chloro-2-phenylbenzoxazole (**5m**).*[6g] Yield: 41 mg (89%). White solid. The spectroscopic data were in good agreement with those of **5m** obtained via the oxidative cyclization of imine **3m**.

*4.4.6. 2-(2-Furyl)-benzoxazole (**5n**).*[10d] Yield: 33 mg (90%). R_f=0.6 (EtOAc/hexanes=1:5). Dark brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.75–7.78 (m, 1H), 7.67 (s, 1H), 7.55–7.58 (m, 1H), 7.34–7.37 (m, 2H), 7.28 (d, J=3.57 Hz, 1H), 6.62–6.63 (m, 1H).

*4.4.7. 2-(2-Thienyl)-benzoxazole (**5o**).*[4b] Yield: 34 mg (86%). R_f=0.6 (EtOAc/hexanes=1:5). Red-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.92 (d, J=3.57 Hz, 1H), 7.72–7.75 (m, 1H), 7.54–7.57 (m, 2H), 7.33–7.36 (m, 2H), 7.20 (t, J=4.67 Hz, 1H).

*4.4.8. 2-(tert-Butyl)-benzoxazole (**5p**).*[10d] Yield: 28 mg (81%). R_f=0.7 (EtOAc/hexanes=1:10). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.68–7.71 (m, 1H), 7.47–7.50 (m, 1H), 7.28–7.31 (m, 2H), 1.50 (s, 9H).

*4.4.9. 2-Cyclohexylbenzoxazole (**5q**).*[10e] Yield: 33 mg (80%). R_f=0.6 (EtOAc/hexanes=1:10). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.67–7.70 (m, 1H), 7.46–7.49 (m, 1H), 7.28–7.31 (m, 2H), 2.92–3.00 (m, 1H), 2.15–2.19 (m, 2H), 1.60–1.89 (m, 5H), 1.24–1.49 (m, 3H).

*4.4.10. 2-Hexylbenzoxazole (**5r**).*[10d] Yield: 31 mg (76%). R_f=0.7 (EtOAc/hexanes=1:10). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.65–7.68 (m, 1H), 7.46–7.49 (m, 1H), 7.28–7.31 (m, 2H), 2.93 (t, J=7.42 Hz, 2H), 1.89 (p, J=7.69 Hz, 2H), 1.30–1.45 (m, 6H), 0.89 (s, 3H).

4.5. General procedures for synthesis of benzothiazoles 8 (Table 6)

2-Aminothiophenol **7** (25 mg; 0.20 mmol; 1.0 equiv) and aldehyde **2** (0.02 mmol; 1.0 equiv), and molecular sieve (10 mg) were dissolved in DMF (1.0 mL). The reaction mixture was stirred at 60 °C. After the complete consumption of the aldehyde, the mixture was cooled to room temperature and NaCN (1.0 mg; 0.020 mmol; 10 mol %) was added to the above reaction mixture and the reaction progress was monitored by TLC. On completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica to give the corresponding benzothiazole **8**.

*4.5.1. 2-Phenylbenzothiazole (**8a**).*[2h] Yield: 35 mg (83%). R_f=0.6 (EtOAc/hexanes=1:9). White solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.09–8.13 (m, 3H), 7.92 (d, J=7.97 Hz, 1H), 7.49–7.52 (m, 4H), 7.40 (t, J=7.69 Hz, 1H).

*4.5.2. 2-(4-Methoxyphenyl)-benzothiazole (**8b**).*[2h] Yield: 39 mg (80%). R_f=0.4 (EtOAc/hexanes=1:9). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.02–8.05 (m, 3H), 7.88 (d, J=7.97 Hz, 1H), 7.47 (t, J=7.14, 1H), 7.36 (t, J=7.14, 1H), 7.00 (d, J=8.79 Hz, 2H), 3.89 (s, 3H).

*4.5.3. 2-(4-Methylphenyl)-benzothiazole (**8c**).*[2h] Yield: 34 mg (76%). R_f=0.6 (EtOAc/hexanes=1:9). Light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.06 (d, J=7.97 Hz, 1H), δ 7.99 (d, J=8.24 Hz, 2H), δ 7.90 (d, J=7.69 Hz, 1H), 7.49 (t, J=7.14 Hz, 1H), 7.37 (t, J=7.14 Hz, 1H), 7.30 (d, J=7.97 Hz, 2H), 2.43 (s, 3H).

*4.5.4. 2-(4-Chlorophenyl)-benzothiazole (**8d**).*[2h] Yield: 45 mg (91%). R_f=0.6 (EtOAc/hexanes=1:9). Light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.02–8.09 (m, 3H), 7.92 (d, J=7.97 Hz, 1H), 7.46–7.54 (m, 3H), 7.41 (t, J=7.97 Hz, 2H).

*4.5.5. 2-(4-Acetylphenyl)-benzothiazole (**8e**).*[2h] Yield: 51 mg (95%). R_f=0.4 (EtOAc/hexanes=1:7). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.17 (m, 4H), 8.11 (d, J=7.97 Hz, 1H), 7.94 (d, J=7.69 Hz, 1H), 7.53 (t, J=7.42 Hz, 1H), 7.43 (t, J=7.42 Hz, 1H), 3.97 (s, 3H).

*4.5.6. 2-(2-Methylphenyl)-benzothiazole (**8f**).*[2h] Yield: 38 mg (84%). R_f=0.5 (EtOAc/hexanes=1:9). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.11 (d, J=7.97 Hz, 1H), 7.94 (d, J=7.97 Hz, 1H), 7.76 (d, J=7.69 Hz, 1H), 7.52 (t, J=7.14 Hz, 1H), 7.42 (t, J=7.14 Hz, 1H), 7.30–7.36 (m, 3H), 2.66 (s, 3H).

*4.5.7. 2-(2-Methoxyphenyl)-benzothiazole (**8g**).*[2e] Yield: 40 mg (83%). R_f=0.4 (EtOAc/hexanes=1:9). White solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.53 (dd, J=7.69, 1.65 Hz, 1H), 8.09 (d, J=7.97 Hz, 1H), 7.93 (d, J=7.97 Hz, 1H), 7.44–7.52 (m, 2H), 7.37 (t, J=7.69 Hz, 1H), 7.14 (t, J=7.69 Hz, 1H), 7.08 (d, J=8.52 Hz, 1H), 4.07 (s, 3H).

*4.5.8. 2-(2-Naphthyl)-benzothiazole (**8h**).*[2e] Yield: 41 mg (79%). R_f=0.6 (EtOAc/hexanes=1:10). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.58 (s, 1H), 8.22 (dd, J=8.52, 1.65 Hz, 1H), 8.12 (d, J=7.97 Hz, 1H), 7.94–8.00 (m, 3H), 7.88–7.91 (m, 1H), 7.55–7.58 (m, 2H), 7.51 (d, J=7.14 Hz, 1H), 7.42 (t, J=7.14 Hz, 1H).

*4.5.9. 2-(2-Furyl)-benzothiazole (**8i**).*[7b] Yield: 32 mg (79%). R_f=0.5 (EtOAc/hexanes=1:9). Light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.05 (d, J=7.97 Hz, 1H), 7.90 (d, J=7.97 Hz, 1H), 7.61 (s, 1H), 7.50 (t, J=7.14 Hz, 1H), 7.39 (t, J=7.14 Hz, 1H), 7.20 (d, J=3.30 Hz, 1H), 6.61 (m, 1H).

*4.5.10. 2-(2-Thionyl)-benzothiazole (**8j**).*[7b] Yield: 25 mg (58%). R_f=0.5 (EtOAc/hexanes=1:9). Light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.03 (d, J=7.97 Hz, 1H), 7.86 (d, J=7.97 Hz, 1H), 7.66 (d, J=3.57 Hz, 1H), 7.45–7.52 (m, 2H), 7.37 (t, J=7.14 Hz, 1H), 7.14 (t, J=3.85 Hz, 1H).

*4.5.11. 2-(tert-Butyl)-benzothiazole (**8k**).*[10d] Yield: 20 mg (52%). R_f=0.7 (EtOAc/hexanes=1:10). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.99 (d, J=7.97 Hz, 1H), 7.85 (d, J=7.69 Hz, 1H), 7.45 (t, J=7.69 Hz, 1H), 7.34 (t, J=7.42 Hz, 1H), 1.53 (s, 9H).

*4.5.12. 2-Cyclohexylbenzothiazole (**8l**).*[3g] Yield: 27 mg (62%). R_f=0.7 (EtOAc/hexanes=1:10). Light colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.97 (d, J=7.97 Hz, 1H), 7.85 (d, J=7.69 Hz, 1H), 7.45 (t, J=7.14 Hz, 1H), 7.34 (t, J=7.14 Hz, 1H), 3.11 (tt, J=11.57. 3.54 Hz, 1H),

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2.17–2.22 (m, 2H), 1.86–1.92 (m, 2H), 1.75–1.79 (m, 1H), 1.58–1.67 (m, 2H), 1.25–1.52 (m, 3H).

*4.5.13. 2-Hexylbenzothiazole (**8m**).*[2j] Yield: 25 mg (57%). R_f=0.7 (EtOAc/hexanes=1:10). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.97 (d, J=8.24 Hz, 1H), 7.84 (d, J=7.97 Hz, 1H), 7.45 (t, J=7.14 Hz, 1H), 7.34 (t, J=7.14 Hz, 1H), 3.11 (t, J=7.69 Hz, 2H), 1.88 (p, J=7.56 Hz, 2H), 1.31–1.44 (m, 6H), 0.89 (t, J=6.87 Hz, 3H).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.138.

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