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Bienzymatic synthesis of benzothia/(oxa)zoles in aqueous medium

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ABSTRACT

A series of 2-arylbenzothiazoles and 2-arylbenzoxazoles were synthesized by the reactions of aldehydes and 2-aminothiophenol and 2-hydroxythiophenol, respectively, using glucose oxidase (GOX)–chloroperoxidase (CPO) catalytic system under oxygen atmosphere.

Benzothiazoles and benzoxazoles are a class of heterocycles that possess diverse array of biological properties (Fig. 1).[1] More particularly, 2-substituted benzothia/(oxa)zoles are of great interest as these structural frameworks have proved to be an important class of privileged bicyclic substructures owing to their potent utility as imaging agents for Ca2þ channel antagonist,[2] β-amyloid, antituberculosis, chemiluminescent agents, calcium channel antagonists, antitumor, antiparasitic, and photosensitizers.[3]

Due to such large potential of 2-substituted benzothia/(oxa)zoles a number of methods were developed for their synthesis. In general, benzothia/(oxa)zoles are synthesized by condensation of 2-amino/hydroxy benzenethiol with carboxylic acid derivatives,[4] the base-induced cyclization of the corresponding 2-haloanilides,[5] or the radical cyclization of thioacylbenzanilides.[6] A number of catalysts, namely, (pmIm)Br,[7] I_2,[8] $ZrOCl_2{\cdot}8H_2O$,[9] TMSCl,[10] PCC,[11] and CAN[12], have been used in the cyclocondensation of 2-amino/hydroxy thiophenol and aldehydes.[13] Recently we have also reported the diversity-oriented synthesis of benzothia/(oxa)zoles by polymer-supported hypervalant iodine reagent. Many of these reported methods have limitations such as drastic reaction conditions,

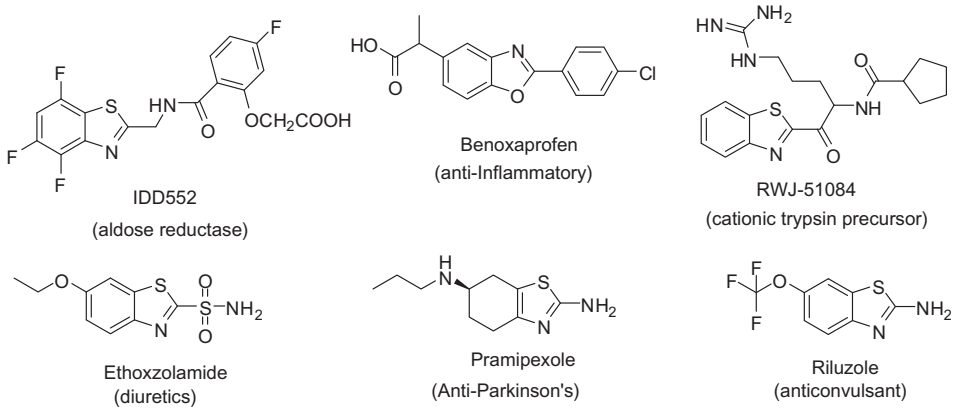

Figure 1. Some biologically active benzothia/(oxa)zoles.

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tedious work-up, possibility of side reactions, and generation of environmentally sustainable acidic/metallic wastes and hardly considered as environmentally benign methods. Therefore, there is an urgent need to overcome the above limitations by developing an efficient and convenient methodology for the synthesis of benzothia/(oxa)zoles.

Biocatalysis is one of the oldest chemical transformations known to humans. Recently the use of enzymes and whole cells for the synthesis of fine chemicals and optically active compounds is tremendously increasing. The major advantages associated with biocatalysts are that they are safe from environmental point of view. Moreover, in biocatalysis non-natural compounds could be utilized as substrates and regio as well as stereo-specific reactions could be performed under mild conditions.

As part of our current interest toward the development of environmentally friendly synthetic protocols for medicinally important heterocycles,[14] we report here a biocatalytic approach for efficient synthesis of 2-substituted benzothiazoles.

In last decades, chloroperoxidase (CPO) from *Caldariomyces fumago* have been shown to catalyze a variety of synthetically useful oxygen transfer reactions with H_2O_2,[15] for example, asymmetric epoxidation of olefins,[16] benzylic, propargylic, and allylic, hydroxylation,[17] asymmetric sulfoxidation,[18] and oxidation of indoles to the corresponding 2-oxindoles.[19] However, a major shortcoming of all heme-dependent peroxidases, such as CPO, is their low operational stability[20] resulting from facile oxidative degradation of porphyrin ring. Thus, continuous addition of hydrogen peroxide, using a syringe, or a pump, was used. However, the rate of addition of the oxidants has to be carefully tuned to keep hydrogen peroxide concentration as low as possible. In recent years, in order to rule out these difficulties, slow and continuous generation of hydrogen peroxide in the reaction mixture has been developed as the substitute of external hydrogen peroxide addition. Glucose oxidase (GOX) is a well-known flavoenzyme which catalyzes the oxidation of β-D-glucose by oxygen to δ-D-gluconolactone and hydrogen peroxide. The enzyme is readily commercially available as it is extensively utilized in food industry and in biosensor for the detection of glucose. The advantage of the hydrogen peroxide generation has been taken in many peroxidase-mediated oxidations.[21]

Here, we report a bienzymatic approach in which in situ-generated hydrogen peroxide was utilized by the peroxidase for the synthesis of benzothia/(oxa)zoles in highly environmentally benign condition (Scheme 1).[22]

In a model reaction, the synthesis of compound **3a** was achieved in order to know the minimum quantity of glucose oxidase–peroxidase (GOX/CPO) ratio. Several GOX/CPO ratios were used to optimize the reaction condition but the best results were obtained with large amount of CPO used for the optimal condition and indicate that all the hydrogen peroxides were used through the peroxidase. The optimum pH range for the glucose oxidase was 5.5–7.0, therefore we used pH 6.0 for the model reaction.[18d] The results of this study were shown in Table 1.

Table 1
Effect of the ratio of bienzymatic system used for the synthesis of **3a**[a]

Entry	GOX(U)	CPO (μmol)	Yield (%)
1	0	0	0[b]
2	1	0.25	38
3	3	0.25	57
4	4	0.25	71
5	8	0.25	63
6	4	0.5	96
7	8	0.5	55

[a] Citrate buffer (pH 6.0) was used as solvent for the optimization of the catalytic system.
[b] 85% yield of compound **5** was obtained .

Table 2
Biocatalytic synthesis of benzothiazoles[a]

Entry	R	Product	Time (h)	Yield (%)
1	C_6H_5	**3a**	12	96
2	4-$CH_3OC_6H_4$	**3b**	12	95
3	4-$CH_3C_6H_4$	**3c**	12	93
4	4-$(CH_3)_2NC_6H_4$	**3d**	12	94
5	4-ClC_6H_4	**3e**	12	95
6	2-ClC_6H_4	**3f**	12	94
7	4-FC_6H_4	**3g**	12	96
8	4-$NO_2C_6H_4$	**3h**	12	97
9	2-Furyl	**3i**	12	93
10	2-Pyridyl	**3j**	12	94

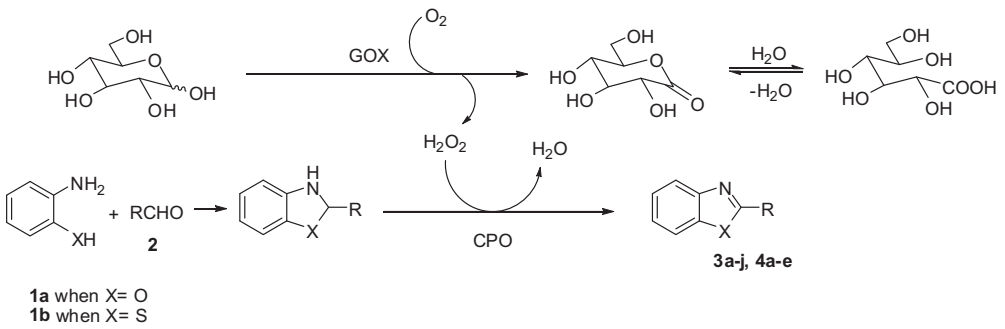
[a] Citrate buffer (pH 6.0) was used as a solvent.

To facilitate the reaction condition several aldehydes were used to synthesize the 2-arylbenzothiazoles using GOX–CPO in citrate buffer under oxygen atmosphere (Table 2).

A variety of aldehydes containing electron-donating and electron-withdrawing groups were successfully employed to prepare the corresponding benzothiazoles. No significant substituent effect was observed on the yields of the products. Heterocyclic aldehydes, such as furaldehyde and pyridine-2-carboxaldehyde, reacted smoothly with 2-aminothiophenol to yield the respective benzothiazoles (Table 2, entries 9 and 10) in excellent yields.

Some of the benzooxazole derivatives have been synthesized in excellent yield via GOX–CPO system, which shows the further applicability of our protocol (Table 3).

In order to know the operational simplicity of the catalytic system, we have also used 2-phenyl-2,3-dihydrobenzo[*d*]thiazole as a substrate. In the optimized reaction condition 2-phenyl-2,3-dihydrobenzo[*d*]thiazole efficiently converted into the corresponding aromatized product **3a** (Scheme 2). This result indicated the utility of GOX–CPO catalytic system in the aromatization of compound **5**.

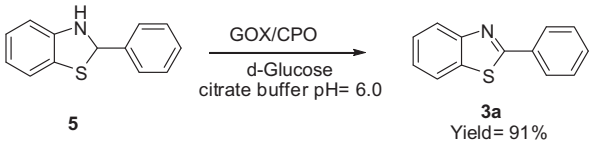


Scheme 1. Bienzymatic synthesis of benzothia/(oxa)zoles.

Table 3
Biocatalytic synthesis of benzoxazoles[a]

Entry	R	Product	Time (h)	Yield (%)
1	C_6H_5	**4a**	12	91
2	4-$CH_3OC_6H_4$	**4b**	12	94
3	4-$CH_3C_6H_4$	**4c**	12	98
4	4-$(CH_3)_2NC_6H_4$	**4d**	12	98
5	4-ClC_6H_4	**4e**	12	89

[a] Citrate buffer (pH 6.0) was used as a solvent.



Scheme 2. Synthesis of **3a** from 2-phenyl-2,3-dihydrobenzo[*d*]thiazoles.

In conclusion we have developed a highly efficient and environment friendly protocol for the synthesis of 2-substituted benzothia/(oxa)zoles. We believe that our methodology may also be applicable for the synthesis of a wide range of heterocycles.

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22. *General experimental procedure for enzymatic synthesis of 2-substituted benzothiazoles*: In a 25 ml round-bottomed flask, 2-aminothiophenol (0.1 mmol), aldehyde (0.1 mmol), and 0.5 ml citrate buffer (pH 6.0) were taken and stirred for 10 min. Then, D-glucose (0.2 mmol in 0.5 ml), Glucose oxidase, Chlorooxidase, and citrate buffer (pH 6.0) were taken and stirred for 12 h under oxygen atmosphere. The reaction was followed by TLC monitoring. After completion of the reaction, the crude was extracted with ethyl acetate and the organic phase was evaporated. The solid obtained was recrystallized from methanol. Spectral data for 2-phenylbenzo[*d*]thiazoles. Physical state: solid $R_f = 0.47$ (1/9 ethyl acetate/hexanes). ESI-MS (m/z) = 212.2 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.16 (m, 3H), 7.92 (d, J = 8.0 Hz, 1H), 7.42–7.53 (m, 4H), 7.39 (d, J = 8.0 Hz, 1H). Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63. Found: C, 73.83; H, 4.33; N, 6.65. Spectral data for 2-phenylbenzo[*d*]oxazoles. Physical state: solid $R_f = 0.43$ (1/9 ethyl acetate/hexanes). ESI-MS (m/z) = 196.1 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.25–8.30 (m, 2H), 7.75–7.80 (m, 1H), 7.50–7.56 (m, 3H), 7.58–7.68 (m, 1H), 7.33–7.40 (m, 2H). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.94; H, 4.58; N, 7.25.