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Photocatalysis by 3,6-Disubstituted-*s*-Tetrazine: Visible-Light Driven Metal-Free Green Synthesis of 2-Substituted Benzimidazole and Benzothiazole

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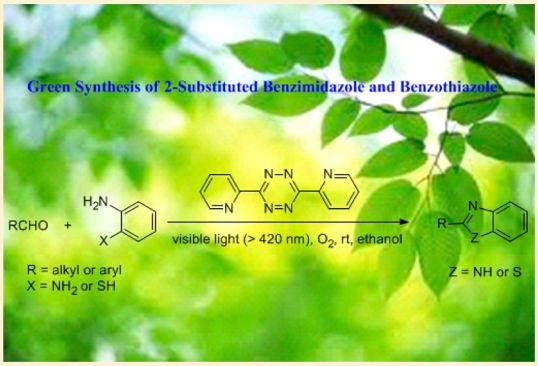
Supporting Information

ABSTRACT: *s*-Tetrazine based molecules were prepared for visible-light-driven organic transformations. The 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**pytz**) derivative shows visible light absorption and reversible one-electron reduction behavior. In the presence of **pytz** and aerial oxygen, aldehyde reacts with *o*-phenylenediamine or *o*-aminothiophenol under visible light irradiation at ambient temperature to produce corresponding 2-substituted benzimidazoles and benzothiazoles, respectively. **Pytz** catalyst demonstrates excellent catalytic activity for alkyl, aryl, organo-metallic substituted aldehydes and reducing sugar. The reaction yield is high for both the electron-donating and electron withdrawing substituents in aromatic aldehydes. The use of a metal-free catalyst and visible light energy, along with the mild reaction conditions, makes this reaction an environmentally benign and energy-saving chemical process.



INTRODUCTION

In recent times, energy issues have become so important that many scientific investigations have sought the development of new sustainable energy resources.[1] The use of solar energy is the most useful alternative sustainable energy source as its abundance is "virtually unlimited" and free. It is also well known that solar light contains 43% visible light.[2] So, the use of visible light to drive organic reactions provides an energetically beneficial pathway for green synthesis.[3] Although most common organic molecules do not absorb light in the visible region, through photosynthesis, nature has shown us the use of various visible light absorbing chromophores for conversion of the solar energy to chemical energy. This inspires the scientific communities to apply visible light in organic synthesis. The recent works on photoredox catalysis by MacMillan and Nicewicz,[4] Yoon,[5] and the Stephenson[6] group have attracted significant attention in this field. Numerous new exciting visible light photochemical processes sensitized by polypyridyl metal complexes, organic dye, or mpg-C_3N_4 photoredox catalysts have been reported since then.[7]

Among *N*-containing heteroaromatic compounds, benzimidazole, benzothiazole, and its derivatives are vital core structures used to create drugs and materials. They exhibit biological activities such as anticancer,[8] antiulcer,[9] antihypertensive,[10] antibacterial,[11] enzyme inhibition,[12] antitumor,[13] antiparasitics,[14] and anticonvulsive ones.[15] Benzimidazole derivatives also exhibit significant activity against several viruses such as HIV,[16] herpes (HSV-1),[17] RNA,[18] influenza,[19] and human cytomegalovirus (HCMV).[16] Drugs having a benzimidazole ring include proton-pump inhibitors (omeprazole), AT1 receptor antagonists (candesartan, telmisartan), direct thrombin inhibitor dabigatran, H1 receptor antagonist mizolastin, and anthelmintic agent such as albendazole, mebendazole, etc. (Supporting Information Figure S1). On the other hand, benzothiazole rings are found in the sodium-channel blocker riluzole, aldol reductase inhibitors IDD552, and cationic trypsin precursor RWJ-51084 (Supporting Information Figure S1). They are also showing interesting utility in dyes,[20] chemosensing,[21] and corrosion science[22] as well as in advanced material science such as nonlinear optics (NLO),[23] organic light-emitting diodes (OLED),[24] and liquid crystals.[25]

Typically, the synthesis of these 1,3-benzazole scaffolds involves the treatment of 1,2-phenylenediamine or *o*-aminothiophenols either with carboxylic acids under strongly acidic conditions or with aldehydes under oxidative conditions. Several oxidative and catalytic reagents, 1,4-benzoquinone,[26] $PhI(OAc)_2$,[27] heteropoly acids,[28] thionyl chloride-treatment,[29] H_2O_2/HCl,[30] iodine,[31] air/dioxane,[32] sulfamic acid,[33] $FeCl_3 \cdot 6H_2O$,[34] $In(OTf)_3$,[35] $Yb(OTf)_3$,[36] $Sc(OTf)_3$,[37] $Cu(OTf)_2$,[38] $KHSO_4$,[39] ionic liquids,[40] (bromo dimethyl) sulfoniumbromide,[41] $ZrOCl_2 \cdot 8H_2O$,[42] $HfCl_4$,[43] copper complex,[44] polymer-supported hypervalent iodine,[45] TsOH/graphite and *N*,*N*-dimethylaniline/graphite,[46] cobalt(III) salen complex on activated carbon,[47] cobalt(II) chloride hexahydrate,[48] VO(acac)$_2$-$CeCl_3$ combo catalyst,[49] gold/CeO_2,[50] nanoporous aluminosilicate AlKIT-5,[51] $Co(OH)_2$/CoO(II),[52] and CuO-np/SiO_2[53] have been employed as catalysts for the synthesis of benzimidazoles from various aldehydes. In the literature, various reagents and catalysts have also been reported for the

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synthesis of 2-substituted benzothiazoles involving the condensation of *o*-aminothiophenols with substituted aldehydes such as I_2,[54] TMSCl,[55] H_2O_2,[56] $H_2O_2/Fe(NO_3)_3$,[57] Dowex 50W,[58] ionic liquids[59] under microwave irradiation, silica gel,[60] $Sc(OTf)_3$,[61] PEG 400,[62] H_2O_2/CAN,[63] trichloroisocyanuric acid (TCCA),[64] and NH_4Cl.[65]

Although the reaction was efficiently carried out by the above catalysts or reagents, some of these methods suffer from one or more disadvantages, such as usage of stoichiometric or larger quantity of reagent, high cost of the catalysts, prolonged reaction times, occurrence of side reactions, severe reaction conditions, and strong oxidizing nature of the reagents and the protocol often involved metal salts, which are toxic toward our environment. Especially, the preparation of substituted benzimidazole and benzothiazoles under metal-free conditions is highly desirable for pharmaceutical purposes due to the low threshold residual tolerance of metals. Therefore, the investigation to search for mild and practicable, stable, cheap, and eco-friendly green synthetic methods of 2-substituted benzimidazoles and benzothiazoles continues to attract the attention of researchers. Recently, Nguyen et al. reported[66] green synthesis of 2-substituted benzimidazoles from benzylamines in the presence of O_2 and acetic acid. An efficient method for synthesis[67] of the 2-substituted benzothiazoles from variety of aldehydes has been developed in presence of $[Ru(bpy)_3Cl_2]$, O_2, and visible light irradiation.

In our continuous effort to exploit visible light to synthesis azole based heterocycles,[68] herein we report simple, efficient, and eco-friendly synthesis of 2-substituted benzimidazoles and benzothiazoles at ambient temperature from various alkyl and aryl aldehydes under visible light irradiation using 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**pytz**) as catalyst (Figure 1).

Figure 1. *s*-Tetrazines exploited for the synthesis of 2-substituted benzimidazole and benzothiazole from various aldehydes.

RESULTS AND DISCUSSION

The first synthesis of the *s*-tetrazines was reported by Pinner[69] at the end of the 19th century. *s*-Tetrazines are highly colored (because of a low-lying π^* orbital leading to a n−π^* transition in the visible region) and electroactive heterocycles that display a very high electron affinity,[70] which makes them easily reducible (actually they are the electron poorest C−N heterocycles). These molecules have been widely used as dienes in inverse electron demand Diels−Alder reactions,[71] and to develop nitrogen-rich energetic materials.[72] Photophysical properties of some substituted tetrazines with a high fluorescence quantum yield and good chemical and photochemical stability have also been thoroughly investigated.[73−76] *s*-Tetrazines have a strong electron-deficient character. Thus, *s*-tetrazines substituted by heteroatoms[73,75,77] and aromatics[78] can be reduced easily in organic solvents to accept one electron to give an anion radical. This reducing nature of the *s*-tetrazines is even more pronounced for the first excited state, which therefore has a relatively strong oxidizing power. Consequently, *s*-tetrazines interact with various electron donor substrates at an excited state.

Considering the visible light absorption behavior and reversible one-electron reduction properties, we have synthesized 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**pytz**) and 3,6-diphenyl-1,2,4,5-tetrazine (**phtz**)[70a,78,79] and applied to the photocatalytic synthesis of 2-substituted benzimidazoles and benzothiazoles from different aldehydes. The optical and electrochemical properties of the **pytz** molecule were studied by UV−vis absorption spectroscopy and cyclic voltammetry. **Pytz** exhibits maximum absorption peaks at 535 nm (ε = 235 M^{-1} cm^{-1}, Figure 2a) and a quasi-reversible reduction peak ($\Delta E_{1/2}$ = 90 mV) at 160 mV in ethanol (Figure 2b). On the other hand, **phtz** shows absorption maxima at 550 nm (ε = 660 M^{-1} cm^{-1}, Supporting Information Figure S1a) and a quasi-reversible reduction peak ($\Delta E_{1/2}$ = 225 mV, Supporting Information Figure S1b) at −385 mV in ethanol. These results clearly demonstrate that presence of two pyridine rings makes tetrazine moiety highly electron deficient, hence, facilitating easy reduction of tetrazine ring.

Initial attempts to optimize the reaction conditions for the synthesis of 2-substituted benzimidazoles, were performed with benzaldehyde as a model substrate in the presence of **pytz**, *o*-phenylenediamine and solvents (Table 1). In a typical experiment, a mixture of *o*-phenylenediamine (1 mmol) and benzaldehyde (1 mmol) in 20 mL ethanol (EtOH) was irradiated under visible light in presence of 1 mg (0.0042 mol %) catalyst for 1−3 h. The effect of reaction time, solvent and amount of

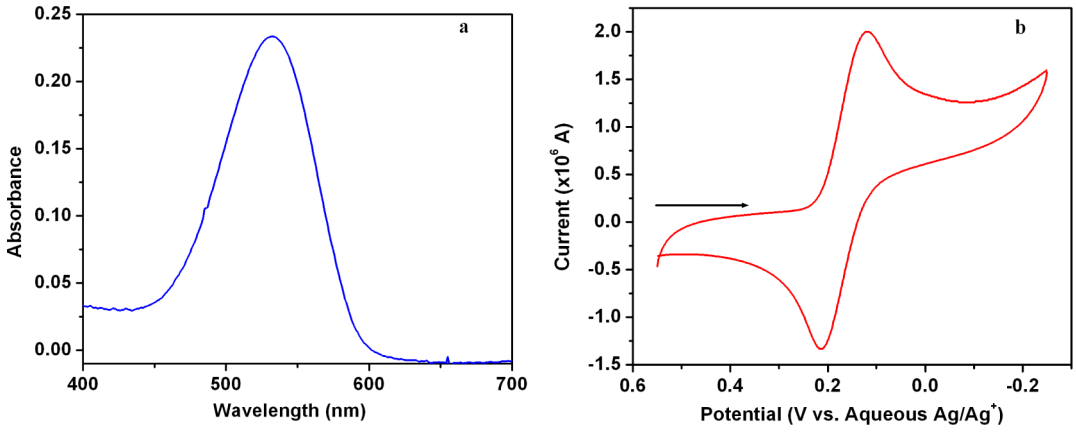

Figure 2. UV−vis absorption spectra (a) and cyclic voltammogram (CV) (b) of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**pytz**) in ethanol. Scan rate for cyclic voltametic measurement is 50 mVs^{-1}.

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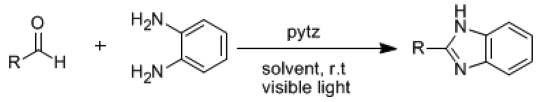
Table 1. Optimization of Reaction Conditions for the Synthesis of 2-Substituted Benzimidazole[a]



entry	catalyst	solvent[b]	time (h)	amount of catalyst (mg)	yield (%)	TON[c]
1	**pytz**	EtOH	2.0	1.0	90	212
2	**pytz**	EtOH	2.0	2.0	90	106
3	**pytz**	EtOH	2.0	3.0	90	70
4	**pytz**	EtOH	1.0	1.0	60	141
5	**pytz**	EtOH	3.0	1.0	90	212
6	**pytz**	MeOH	2.0	1.0	80	189
7	**pytz**	THF	2.5	1.0	30	71
8	**pytz**	CH_3Cl	2.5	1.0	30	71
9	**pytz**	CH_2Cl_2	2.0	1.0	60	141
10	**pytz**	CH_3CN	2.5	1.0	30	71
11	**pytz**	DMF	3.0	1.0	10	24
12	**pytz**	DMSO	2.0	1.0	40	94
13	**phtz**	EtOH	2.0	1.0	40	94
14[d]	**pytz**	EtOH	2.0	1.0	00	00
15[e]		EtOH	2.0			
16[f]	**pytz**	EtOH	2.0	1.0	90	212

[a]Reaction Conditions: benzaldehyde (1 mmol), *o*-phenylenediamine (1 mmol). [b]20 mL of solvent used for all reactions. [c]The moles of 2-substituted benzimidazole formed per mol catalyst. [d]Reaction carried out in absence of visible-light (dark). [e]Reaction carried out without any catalyst but in presence of visible-light. [f]Reaction Conditions: benzaldehyde (2 mmol), *o*-phenylenediamine (1 mmol).

catalyst on the reaction was evaluated thoroughly. The optimum reaction conditions are 2 h and in presence of 1 mg catalyst in ethanol. Further prolonging the reaction time or increasing the amount of catalyst will not improve the yield of the reaction. The solvent has a prominent influence on the yield (Table 1). The experimental results show that ethanol is a good solvent with above 90% yield. (Table 1, entries 1−5). However, tetrahydrofuran (entry 7), chloroform (entry 8), dichloromethane (entry 9), acetonitrile (entry 10), dimethyl formamide (entry 11), and dimethyl sulfoxide (entry 12) are not suitable for the reaction and methanol (entry 6) show moderately high yield. To ascertain that visible light is necessary (as shown in proposed mechanism later on) for the reaction to proceed, a control reaction was carried out in the dark in presence of **pytz**. In absence of visible light, **pytz** shows no catalytic activity (entry 14), which clearly demonstrates the role of visible light in this reaction. Similarly, a control reaction in the absence of **pytz** did not proceed under identical conditions (entry 15). To compare catalytic activity of the 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**pytz**) with the 3,6-diphenyl-1,2,4,5-tetrazine (**phtz**), we have also investigated the catalytic activity of **phtz** under identical conditions (entry 13). **Phtz** shows much inferior activity.

Although the reaction of *o*-phenylenediamine with aldehydes in the presence of various catalysts has been exploited to build the benzimidazole scaffold, the issue of selectivity still remains critical due to the competitive formation of 1,2-disubstituted and 2-substituted benzimidazoles. It can be observed that current protocol is completely selective toward formation of 2-substituted benzimidazole with excellent yield. The use of 2 equiv of benzaldehyde also afforded 2-substituted benzimidazole (Table 1, entry 15) as the sole product and indicated the ability of **pytz** to drive the selectivity toward 2-substituted product.

This reaction meets many of the requirements of green chemistry: (a) a very low E-factor[80] was achieved because minimal waste is generated; (b) high atom-economy is achieved; (c) the reaction is driven by visible light and occurs at ambient temperature; (d) the reaction uses molecular oxygen from air as the oxidant; (d) a nonmetal, cheap, and a relatively small quantity of *s*-tetrazine is used as the catalyst; (f) the reaction uses environmentally benign ethanol as the solvent that is easily recycled during workup.

With the optimized protocol, we next set out to explore the scope and limitation of the reaction (Table 2). In order to get an insight into the effect of starting materials on the yield of 2-substituted benzimidazole, several substituted aldehydes including aromatic, heteroaromatic, and aliphatic groups were used as the starting materials; the results are listed in the Table 2. Most of the aldehydes gave excellent yields over 80% and the highest yield of 95% was obtained in the case of salicyldehyde as a starting material (entry 2), while the relatively lower yield of 60% was obtained in the case of heterocyclic aldehyde, 2-pyridine carboxaldehyde (entry 9). Other heterocyclic aldehydes such as 2-thiophene-carboxaldehyde, furfuraldehyde, and 3*H*-imidazole-4-carbaldehyde exhibit even poorer yields. The reaction was also investigated for both the electron-donating or electron-withdrawing substituents in the aromatic ring. The experimental results show that reaction yield is excellent (>90%) for both the electron-donating and electron-withdrawing aromatic substituents. This protocol is also highly efficient for the ferrocenecaboxaldehyde (entry 14). The catalytic TONs and TOFs obtained in the synthesis of different benzimidazole were found to be moderately high.

Encouraged by these results, we further studied to expand the synthetic scope of this protocol and carried out the reaction using *o*-aminothiophenol for the synthesis of 2-substituted benzothiazole. The effect of reaction time, solvent, and amount of catalyst on the reaction was again evaluated thoroughly. Interestingly, solvent and amount of catalyst for the reaction remain same but reaction proceeds within much lower time (20−30 min).

To study the generality of this protocol for the synthesis of 2-substituted benzothiazole, a variety of aromatic, heterocyclic, and aliphatic aldehydes with various substitution patterns were reacted with *o*-aminothiophenol under the optimized conditions to give 2-substituted benzothiazole. As can be seen from Table 3, most of the substrates afforded good yields of the corresponding 2-substituted benzothiazole. In general, the aromatic aldehydes containing electron-donating as well as electron-withdrawing substituent exhibit excellent yield as well as TON, and TOF (Table 3, entries 1−8 and 10−12). Pyridine 2-carboxaldehyde (Table 3, entry 9) was not very suitable for this transformation, giving low yield. Further investigation indicates that aliphatic aldehydes are also suitable for this reaction (Table 3, entries 13−15). Interestingly, the terephthalaldehyde selectively gave the 4-benzothiazole-yl-benzaldehyde (entry 11) as product in excellent yield and selectivity when the reaction was carried out in ethanol medium irrespective of ratio of aldehyde and *o*-aminothiophenol due to lower solubility of 4-benzothiazole-yl-benzaldehyde in ethanol. On the other hand, when the reaction was carried out in tetrahydrofuran medium, exclusively phenyl-1,4-dibenzothiazole (entry 12) was formed. So, this protocol might be useful for

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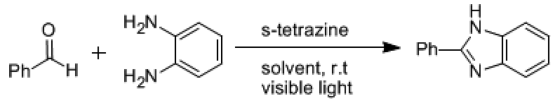
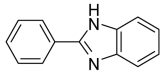
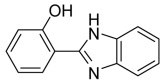
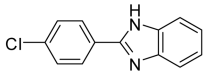
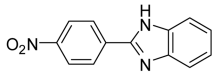
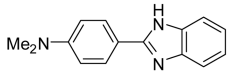
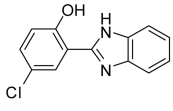
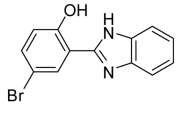
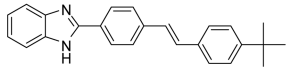
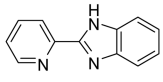
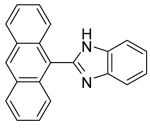
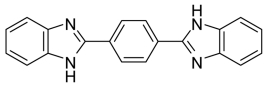
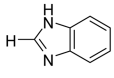
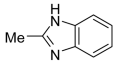
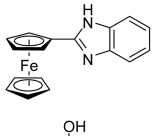
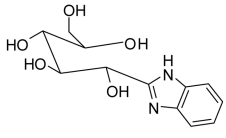
Table 2. Scope of the 3,6-Di(pyridin-2-yl)-1,2,4,5-*s*-tetrazine Catalyzed Synthesis of the 2-Substituted Benzimidazoles[a]



entry	R	product	time (h)	Yield[b] (%)	TON[c]	TOF[d] (h^{-1})
1	C_6H_5		2.0	90	212	106
2	2-(OH)C_6H_4		2.0	95	224	112
3	4-ClC_6H_4		2.0	90	212	106
4	4-(NO_2)C_6H_4		2.5	85	201	80.4
5	4-{(Me_2) N}C_6H_4		2.0	91	215	107.5
6	5-Cl-2-(OH)C_6H_3		2.4	90	212	88.33
7	5-Br-2-(OH)C_6H_3		3.0	87	205	68.33
8	4-[2-(4-tert-Butyl-phenyl)-vinyl]-phenyl		2.5	80	189	75.6
9	2-pyridine		3.0	60	141	47
10	9-anthracene		2.0	90	212	106
11	(1,4)–C_6H_4[e]		2.5	80	189	75.6
12	H		3.0	78	184	61.33
13	Me		3.0	80	189	63
14	ferrocene		2.0	85	201	100.5
15	glucose		2.5	91	215	86

[a]Reaction Conditions: aldehyde (1 mmol), *o*-phenylenediamine (1 mmol), 1 mg catalyst, ethanol 20−30 mL. [b]Isolated yield after purification. [c]The moles of 2-substituted benzimidazole formed per mol catalyst. [d]Rate of the formation of 2-substituted benzimidazole per mol catalyst per unit time. [e]*o*-Phenylenediamine (2 mmol).

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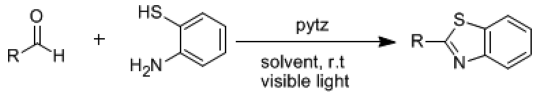
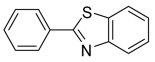
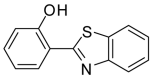
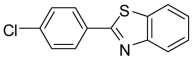
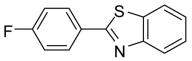
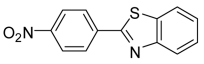
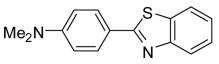
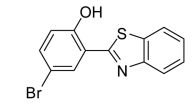
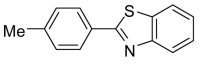
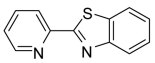
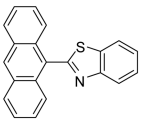
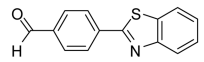
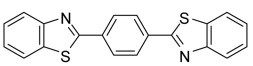
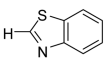
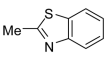
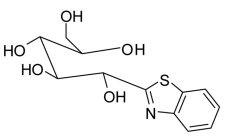
Table 3. Scope of the 3,6-Di(pyridin-2-yl)-1,2,4,5-*s*-tetrazine Catalyzed Synthesis of the 2-Substituted Benzothiazoles[a]



entry	R	product	time (min)	Yield[b] (%)	TON[c]	TOF[d] (h^{-1})
1	C_6H_5		40	90	212	318
2	2-(OH)C_6H_4		30	92	217	434
3	4-ClC_6H_4		45	87	205	273
4	4-FC_6H_4		45	86	203	270
5	4-(NO_2)C_6H_4		45	80	189	252
6	4-(NMe_2)C_6H_4		35	95	224	384
7	5-Br-2-(OH)C_6H_3		36	85	201	335
8	4-MeC_6H_4		40	89	210	315
9	2-pyridine		60	65	153	153
10	9-anthracene		45	80	189	252
11	1-(CHO)C_6H_4		30	85	201	402
12[e]	(1,4)–C_6H_4		60	30	71	71
13	H		45	75	177	236
14	Me		45	78	184	245
15	glucose		50	95	224	268

[a]Reaction Conditions: aldehyde (1 mmol), *o*-aminothiophenol (1 mmol), 1 mg catalyst, ethanol 20−30 mL. [b]Isolated yield after purification. [c]The moles of 2-substituted benzothiazole formed per mol catalyst. [d]Rate of the formation of 2-substituted benzothiazole per mol catalyst per unit time. [e]Solvent: Tetrahydrofuran, *o*-aminothiophenol (2 mmol).

the selective synthesis of mono- or di-benzothiazole from dialdehyde.

Another interesting aspect of our protocol is the synthesis of 2-[(D-gluco-1,2,3,4,5-pentahydroxyl)pentyl]-1*H*-benzimidazole

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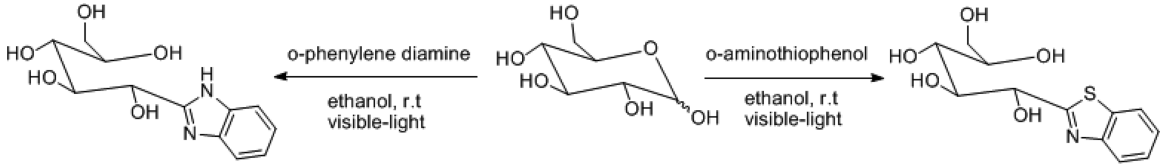
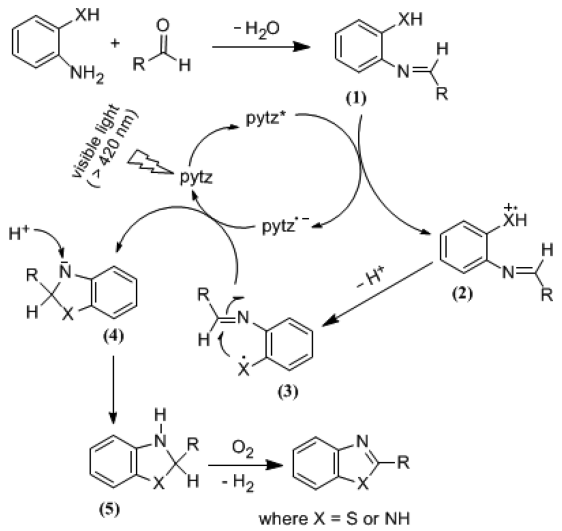
Scheme 1. Synthesis of 2-[(D-Gluco-1,2,3,4,5-pentahydroxyl)pentyl]-1*H*-benzimidazole and 2-[(D-Gluco-1,2,3,4,5-pentahydroxyl)pentyl]-benzothiazole from D-Glucose



(entry 15, Table 2) or benzothiazole (entry 16, Table 3) from D-glucose. Synthesis of sugar-based benzimidazoles was first reported more than one hundred years ago by Griess and Harrow through condensation of D-glucose and *o*-phenylenediamine in the presence of hydrochloric acid to afford the open chain sugar derivative as the minor product, and in fact it was the first report for synthesis of benzimidazoles.[81] Several synthetic routes for the preparation of various aldo-benzimidazoles have been achieved in the intervening years.[82] We describe herein an improved protocol for the synthesis of benzimidazole and benzothiazole by direct condensation of D-glucose, with *o*-phenylenediamine in the presence visible light and **pytz** catalyst in neutral medium (Scheme 1). We are also currently exploring the scope of this protocol for the synthesis of various aldo-benzimidazoles by direct oxidative condensation of aldoses, including mono-, di-, and trisaccharides, with *o*-phenylenediamines in the presence of **pytz** and visible light.

To obtain more insight into the reaction process, we move toward the mechanism of the **pytz**-catalyzed synthesis of 2-substituted benzimidazole or benzothiazole and Scheme 2

Scheme 2. Proposed Reaction Mechanism



illustrates a plausible reaction pathway for this reaction. Audebert and others have reported that *s*-tetrazines have a strong oxidizing power in their ground state which is more pronounced in their first excited state.[70] They even demonstrated that fluorescence of the fluorescent tetrazines are quenched by various electron donors. They also utilized this phenomenon for the fluorimetric sensing of amines by silica nanoparticles grafted on their surface with tetrazine dyes.[83]

Primarily, we investigated whether the imine intermediate is formed prior to formation of benzimidazole or benzothiazole. We have carried out the reaction with preformed imine (monoaldimine intermediate in case of benzimidazole) compound under the same condition and found that the efficiency of the catalyst remains the same. It can also be seen that for those aldehydes that formed imine readily, the reaction time is shorter and the yield is relatively much higher (Table 2 and Table 3). On the other hand, for aldehydes that do not form imine easily, (heterocyclic and aliphatic aldehydes), the reaction time is relatively longer with moderate yield. Now, upon irradiation, **pytz** gets excited to **pytz***, which is reductively quenched by imine intermediate **1** to produce **pytz** radical anion and monoaldimine radical cation **2** via single electron transfer oxidation. The radical cation **2** then yields another radical species **3** after deprotonation. Now, intramolecular nucleophilic attack on C═N carbon atom takes place, followed by regeneration of the catalyst **pytz** through oxidation. Subsequent proton uptake produces hydrogenated cyclized intermediate **5**. Then, oxidative dehydrogenation by air leads to desired benzimidazoles or benzothiazoles.

To confirm the role of O_2 (air) in this process, a reaction was run with benzaldehyde and *o*-aminothiophenol under inert atmosphere in the presence of **pytz** and visible light. The compound that got isolated under inert atmosphere is highly unstable[84] in the presence of air, even in the solid state, and quickly got converted into the corresponding benzothiazole. The FT-IR spectrum of this compound was obtained within a very short time (to avoid interaction with O_2) and compared with the spectrum of pure 2-phenyl benzothiazole. From the FT-IR spectrum (Supporting Information Figure S2) it is evident that the product isolated under inert atmosphere exhibits a strong peak at around 2950 cm^{-1} due to N−H stretching.[84] This peak is absent in pure 2-phenyl benzothiazole (Supporting Information Figure S2).

To prove the radical intermediate, we have carried out the same reaction in the presence of the radical inhibitor TEMPO (Table 2, entry 1 and Table 3, entry 1). It results in a drastic decrease in the yield of the corresponding benzimidazole or benzothiazole, suggesting the possibility of a radical intermediate. Scheme 2 shows the plausible reaction mechanism.

■ CONCLUSION

In conclusion, the present procedure using an easily available *s*-tetrazine, **pytz** provides a very simple and efficient methodology for the synthesis of 2-substituted benzimidazoles or benzothiazoles from aldehydes under visible light irradiation. This procedure also shows excellent yields, selectivity toward 2-substituted benzimidazoles, and does not produce unnecessary waste. Most importantly, the use of renewable resources, such as visible light, air, and an environmentally benign solvent in a highly atom-economical and energy-efficient manner, adheres well to the principles of green chemistry. 3,6-Di(pyridin-2-yl)-1,2,4,5-tetrazine (**pytz**) absorbs visible light and undergoes one electron quasi-reversible reduction at a positive potential. After considering these results, a possible mechanism of this catalytic system is provided. We believe that the strategy of using

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organic molecules that absorb visible light can be expanded to the utilization of solar energy in various metal-free catalytic methodologies in organic synthesis and chemical industry.

EXPERIMENTAL SECTION

General Methods. Solvents were purified according to standard methods prior to use, while all other substances and reagents used were commercially available and used as received. The synthesis of 3,6-di(pyridin-2-yl)-1,2,4,5-*s*-tetrazine (**pytz**) and 3,6-diphenyl-1,2,4,5-tetrazine (**phtz**) were carried out following the method reported earlier.[70a,78,79] A Xenon lamp with a power of 300 W equipped with a cutoff filter (λ > 420 nm) was used as a visible light source. The reaction was carried out in a 100 mL double-walled quartz beaker flask having water inlet and outlet to maintain the room temperature of the reaction vessel. ^{1}H NMR spectra were recorded using 300, 400, and 500 MHz NMR spectrometers, and ^{13}C NMR spectra were measured using a 75 MHz spectrometer. All ^{1}H data were reported in parts per million (ppm) relative to tetramethylsilane (δ_H = 0) in the deuterated solvents. LC−MS were obtained from a liquid chromatography instrument equipped with a mass-selective detector. All GC analyses were performed on a GC system with an FID detector using a J & W HP−5 column (30 m, 0.32 mm internal diameter) and *n*-decane as the internal standard. High-resolution mass spectra were recorded using ESI ionization method with quadrupole time-of-flight MS systems. Cyclic voltammetric (CV) measurement was carried out with a three-electrode assembly comprising glassy carbon working electrode, a platinum auxiliary electrode, and an aqueous Ag/AgCl reference electrode. The concentration of the supporting electrolyte tetramethylammonium perchlorate (TEAP) was 0.1 M, while that of the complex was 1 mM. Under the given experimental conditions, the potential of the external standard ferrocene/ferrocenium (Fc/Fc^+) couple was measured at +0.400 V vs Ag/AgCl. Elemental (C, H, N, and S) analyses were performed on an elemental analyzer (Perkin−Elmer 2400 II). Melting points were determined in open capillaries and are uncorrected.

General Experimental Procedure for the Synthesis of 2-Substituted Benzimidazole. A mixture of aldehyde (1 mmol, 1 equiv), *o*-phenylenediamine (1 mmol, 1 equiv), and catalyst (0.00423 mmol, 1 mg) was taken in a 100 mL double-walled quartz beaker having water inlet and outlet to maintain the temperature of the reaction vessel in ethanol (20 mL). The beaker was exposed to visible light under stirring condition and was allowed to proceed for 2−3 h. The progress of the reaction was monitored by TLC or gas chromatography. After completion of the reaction, solvent was evaporated at reduced pressure and the product was dissolved in minimum volume of ethyl acetate. The solvent was concentrated in vacuo and purified by column chromatography using silica gel (hexane/EtOAc) to get the desired product.

2-Phenyl-1H-benzo[d]imidazole (Table 2, Entry 1[64]). White solid (174 mg, 90%) mp, 291−293 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 12.92 (s, 1H), 8.17 (d, 2H, J = 6.0 Hz), 7.66 (d, 1H, J = 5.2 Hz), 7.56−7.48 (m, 4H), 7.20 (s, 2H).

2-(1H-Benzo[d]imidazol-2-yl)phenol (Table 2, Entry 2[64]). White solid (199 mg, 95%), mp 240−242 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 13.16 (s, 1H), 8.04 (d, 1H, J = 10 Hz), 7.70−7.60 (m, 1H), 7.37 (t, 2H, J = 10 and 9 Hz), 7.27 (s, 2H), 7.03−6.99 (m, 2H).

2-(4-Chlorophenyl)-1H-benzo[d]imidazole (Table 2, Entry 3[64]). White solid (205 mg, 90%), mp 290 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 12.99 (s, 1H), 8.18(d, 2H, J = 10.5 Hz), 7.64 (qt, 3H, J = 9.5, 12, and 11 Hz), 7.52 (d, 1H), 7.24−7.16 (m, 2H).

2-(4-Nitrophenyl)-1H-benzo[d]imidazole (Table 2, Entry 4[40]). Off-white solid (203 mg, 85%), mp 260 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 13.28 (s, 1H), 8.38(m, 4H), 7.71 (d, 1H, J = 9.5 Hz), 7.57 (d, 1H, J = 9.5), 7.25 (dd, 2H, J = 10.5, 3 and 10.5). LC−MS (ESI^+): m/z = 240.00, [100%, MH^+]; Calcd for $C_{13}H_{10}N_3O_2$: 240.07.

4-(1H-Benzo[d]imidazol-2-yl)-N,N-dimethylaniline (Table 2, Entry 5[64]). White solid (215 mg, 91%), mp 272−274 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 7.96 (d, 2H, J = 8.5 Hz), 7.50(s, 2H), 7.13 (s, 2H), 6.80 (d, 2H, J = 8.5 Hz).

2-(1H-Benzoimidazol-2-yl)-5-chlorophenol (Table 2, Entry 6). Off-white solid (219 mg, 90%), mp 305−306 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 13.275 (s, 2H), 8.173 (d, 1H, J = 8.5 Hz), 7.685 (s, 1H), 7.416 (dd, 1H, J = 2.5, 6.5, and 2.5 Hz), 7.309 (d, 2H, J = 8.5 Hz), 7.078 (d, 1H, J = 8.5 Hz).

2-(1H-Benzo[d]imidazol-2-yl)-5-bromophenol (Table 2, Entry 7). Off-white solid (249 mg, 87%), mp 300−302 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 13.28 (s, 2H), 8.28 (t, 1H, J = 1 and 2 Hz), 7.71 (s, 2H), 7.61 (d, 1H), 7.52−7.50 (m, 2H), 7.28 (d, 2H, J = 10 Hz), 7.01 (dd, 1H, J = 1.5, 9.5, and 1 Hz).

2-{4-[2-(4-tert-Butyl-phenyl)-vinyl]-phenyl}-1H benzimidazole (Table 2, Entry 8). White solid (323 mg, 92%), mp 375−377 °C. Anal. Calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 85.23; H, 6.89; N, 7.92. ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 12.83 (s, 1H), 8.09 (d, 2H, J = 8.1 Hz), 7.68 (d, 2H, J = 8.4 Hz), 7.47 (d, 3H, J = 8.4), 7.32 (d, 2H, J = 8.4 Hz), 7.26 (s, 1H), 7.21 (s, 1H), 7.14−7.10 (m, 3H), 1.20 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 151.5, 151.0, 139.1, 134.5, 129.9, 129.3, 127.3, 127.2, 126.8, 126.0, 34.8, 31.5. LC−MS (ESI^+): m/z = 353.00, [100%, MH^+]; Calcd for $C_{25}H_{25}N_2$: 353.20.

2-(Pyridin-2-yl)-1H-benzo[d]imidazole (Table 2, Entry 9[82]). White solid (117 mg, 60%), mp 220−222 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 8.679 (d, 1H, J = 4.4 Hz), 8.862 (d, 2H, J = 8.0 Hz), 7.964 (t, 1H, J = 8.0 and 7.6 Hz), 7.628 (dd, 2H, J = 3.2, 2.4, and 3.2 Hz), 7.484 (t, 1H, J = 5.6 and 6.4 Hz), 7.235 (dd, 1H, J = 3.2, 2.8, and 3.2 Hz).

2-(Anthracen-9-yl)-1H-benzo[d]imidazole (Table 2, Entry 10[40]). Off-white solid (264 mg, 90%), mp 262−263 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 8.825 (s, 1H), 8.51 (d, 2H, J = 10.5 Hz), 7.70 (s, 2H), 7.62 (d, 2H, J = 11 Hz), 7.55 (t, 2H, J = 8 and10 Hz), 7.50 (t, 2H, J = 9 and 9.5 Hz), 7.31 (dd, 2H, J = 3.55 and 4 Hz).

1H-Benzo[d]imidazole (Table 2, Entry 12[85]). White solid (88.5 mg, 75%), mp 170−172 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 12.52 (br, 1H), 8.25 (s, 1H), 7.64−7.58 (m, 2H), 7.22−7.26 (m, 2H). LC−MS (ESI^+): m/z = 119.10, [100%, MH^+]; Calcd for $C_7H_7N_2$: 119.06.

2-Methyl-1H-benzo[d]imidazole (Table 2, Entry 13[86]). White solid (102 mg, 78%), mp 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.82 (s, 1H), 7.60 (s, 2H), 7.26 (s, 2H), 2.70 (s, 3H).

Ferrocene Benzimidazole (Table 2, Entry 14[87]). Yellow solid (256 mg 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 12.38 (s, 1H), 7.53−7.44 (m, 2H), 7.12 (s, 2H), 5.03 (s, 2H), 4.45 (s, 2H), 4.09 (s, 5H). LC−MS (ESI^+): m/z = 303.00, [100%, MH^+]; Calcd for $C_{17}H_{15}N_2Fe$: 303.168.

2-[(D-Gluco-1,2,3,4,5-pentahydroxyl)pentyl]-1H-benzimidazole (Table 2, Entry 15[82a]). Brown solid[81] (243 mg, 91%), mp 213−215 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 12.26 (br, 1H), 7.48 (d, 2H, J = 4.5 Hz), 7.14−7.09 (m, 2H), 4.89 (d, 1H, J = 3.5 Hz), 5.07−4.24 (m, 5H), 3.66−3.32 (m, 6H). LC−MS (ESI^+): m/z = 269.00, [100%, MH^+]; Calcd for $C_{12}H_{17}N_2O_5$: 269.118.

1,4-Di(1H-benzo[d]imidazol-2-yl)benzene (Table 2, Entry 11[48]). This compound was synthesized following the method described for others benzimidazole using 2 equiv of *o*-phenylenediamine. Brown solid (248 mg, 80%), mp 112 °C. ^{1}H NMR (400 MHz, DMSO-d_6) 13.05 (s, 2H), 8.35 (s, 4H), 7.70 (d, 2H, J = 7.6 Hz), 7.57 (d, 2H, J = 7.6 Hz), 7.19−7.26 (m, 4H). HRMS (ESI^+): m/z = 311.2011, [100%, MH^+]; Calcd for $C_{20}H_{15}N_4$: 311.3665.

General Experimental Procedure for the Synthesis of 2-Substituted Benzothiazole. A mixture of aldehyde (1 mmol, 1 equiv), *o*-aminothiophenol (1 mmol, 1 equiv) and catalyst (0.00423 mmol, 1 mg) was taken in ethanol (25 mL) in a 100 mL double-walled quartz beaker. The quartz beaker was exposed to visible light under stirring condition and was allowed to proceed for 30−60 min. The progress of the reaction was monitored by TLC or gas chromatography. After completion of the reaction, ethanol was evaporated at reduced pressure and the product was dissolved in a minimum volume of dichloromethane. The organic layer was dried over dehydrated Na_2SO_4, concentrated in vacuo, and purified by column chromatography using silica gel (hexane/EtOAc) to give the desired product.

2-Phenyl Benzothaizole (Table 3, Entry 1[68]). Yellow solid (203 mg, 96%), mp 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.140−8.100

(m, 3H), 7.849 (d, 1H, J = 6.4 Hz), 7.508−7.453 (m, 4H), 7.358 (t, 1H, J = 5.6 Hz).

2-Benzothiazol-2-yl-phenol (Table 3, Entry 2[68]*).* White crystalline solid (223 mg, 98%), mp 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 12.546 (s, 1H), 7.97 (d, 1H, J = 8 Hz), 7.86 (d, 1H, J = 8 Hz), 7.668 (d, 1H, J = 7.6 Hz), 7.492 (t, 1H, J = 7.6 Hz), 7.389 (t, 2H, J = 7.2 Hz), 7.125 (d, 1H, J = 8.4 Hz), 6.94 (t, 1H, J = 7.2 Hz).

2-(4-Chloro-phenyl)-benzothiazole (Table 3, Entry 3[68]*).* White solid (226 mg, 92%), mp 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.073 (d, 1H, J = 8 Hz), 8.018 (d, 2H, J = 8.4 Hz), 7.896 (d, 1H, J = 8 Hz), 7.516 (d, 1H, J = 7.6 Hz), 7.488 (t, 2H, J = 7.6 Hz), 7.398 (t, 1H, J = 8 Hz).

2-(4-Fluoro-phenyl)-benzothiazole (Table 3, Entry 4[68]*).* White solid (206 mg, 90%), mp 102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.072−8.029 (m, 3H), 7.851 (d, 1H, J = 10.60 Hz), 7.468 (t, 1H, J = 9.87 Hz), 7.352 (t, 1H, J = 9.81 Hz), 7.327−7.118 (m, 2H).

2-(4-Nitro-phenyl)-benzothiazole (Table 3, Entry 5[68]*).* Yellow solid (243 mg, 95%), mp 233 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.362 (d, 2H, J = 9.2 Hz), 8.274 (d, 2H, J = 9.2 Hz), 8.139 (d, 1H, J = 8.4 Hz), 7.969 (d, 1H, J = 8 Hz), 7.566 (t, 1H, J = 7.8 Hz), 7.474 (t, 1H, J = 8 Hz).

(4-Benzothiazol-2-yl-phenyl)-dimethyl-amine (Table 3, Entry 6[68]*).* Light yellow solid (240 mg, 95%), mp 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.981 (m, 3H), 7.845 (d, 1H, J = 8 Hz), 7.443 (t, 1H, J = 7.6 Hz), 7.328−7.264 (m, 1H), 6.748 (d, 2H, J = 8.8 Hz), 3.053 (s, 6H).

2-Benzothiazol-2-yl-5-bromo-phenol (Table 3, Entry 7[68]*).* White solid (290 mg, 95%), mp 170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 11.746 (s, 1H), 8.347 (d, 1H, J = 2.4 Hz), 8.108 (d, 1H, J = 7.6 Hz), 8.047 (d, 1H, J = 8), 7.542−7.503 (m, 2H), 7.444−7.404 (m, 1H), 7.039 (d, 1H, J = 8).

2-p-Tolyl-benzothiazole (Table 3, Entry 8[68]*).* Yellow solid (206 mg, 92%), mp 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.956 (d, 1H, J = 6.4 Hz), 7.836 (d, 2H, J = 6.8 Hz), 7.703 (d,1H, J = 6.4 Hz), 7.328 (t, 1H, J = 6 Hz), 7.202 (t, H, J = 6 Hz), 7.119 (d, 2H, J = 6.4 Hz), 2.248 (s, 3H).

2-Pyridine-2-yl-benzothiazole (Table 3, Entry 9[68]*).* White solid (193 mg, 92%), mp 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.688 (d, 1H, J = 4.8 Hz), 8.289 (d, 1H, J = 8 Hz), 8.117 (d, 1H, J = 8 Hz), 8.066 (d, 1H, J = 8 Hz), 8.010−7.968 (m, 1H), 7.534 (q, 2H, J = 5.2, 7.2, and 7.6 Hz), 7.453 (t, 1H, J = 7.6).

2-Anthracen-9-yl-benzothiazole (Table 3, Entry 10[68]*).* Yellow solid (216 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.643 (s,1H), 8.277 (d, 1H, J = 8 Hz), 8.074 (t, 3H, J = 8.8 Hz), 7.84 (d, 2H, J = 8.8 Hz), 7.643 (t, 1H, J = 7.2 Hz), 7.571−7.7.437 (m, 5H).

4-(Benzothiazol-2-yl)benzaldehyde (Table 3, Entry 11[68]*).* Yellow solid (226 mg, 95%), mp 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.09(s, 1H), 8.308 (d, 2H, J = 8.4 Hz), 8.194 (d, 1H, J = 8.8 Hz), 8.128−8.070 (m, 3H), 7.587 (m, 1H), 7.511 (m, 1H).

Benzothiazole (Table 3, Entry 13[68]*).* Light-yellow liquid (106 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.885 (s, 1H), 8.072−8.029 (m, 1H), 7.852 (d, 1H, J = 10.2 Hz), 7.466 (t, 1H, J = 9.8 Hz), 7.352 (t, 1H, J = 9.8 Hz).

2-Methyl-benzothiazole (Table 3, Entry 14[68]*).* Pale-yellow liquid (123 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.880 (d, 1H, J = 10.8 Hz), 7.752 (d, 1H, J = 10.8 Hz), 7.359 (t, 1H, J = 9.6 Hz), 7.23 (t, 1H, J = 10.8 Hz), 2.769 (s, 3H).

2-[(D-Gluco-1,2,3,4,5-pentahydroxyl)pentyl]-benzothiazole (Table 3, Entry 15). White solid (280 mg, 95%), mp 75−77 °C. Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91; S, 11.24. Found: C, 50.55; H, 5.32; N, 4.92; S, 11.27. ^{1}H NMR (300 MHz, CD_3OD) δ_H 6.96 (d, 1H, J = 10 Hz), 6.86−6.80 (m, 1H), 6.65−6.58 (m, 2H), 4.84 (s, 5H), 3.79−3.58(m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 152.7, 136.2, 125.6, 124.5, 122.0, 121.5, 71.6, 71.4, 68.7, 68.3, 63.2. LC−MS (ESI$^+$): m/z = 285.90, [100%, MH^+]; Calcd for $C_{12}H_{16}NO_5S$: 286.08.

Synthesis of Phenyl-1,4-dibenzothiazole (Table 3, Entry 12[68]*).* In 100 mL double walled quartz beaker, a mixture of terephthaldehyde (0.13 g, 1 mmol), 2-amino thiophenol (0.25 g, 2 mmol) and catalyst (0.00423 mmol, 1 mg) was taken in tetrahydrofuran (20 mL). The reaction mixture was then exposed to visible light and stirred for 60 min. The insoluble product was collected through filtration and washed thoroughly with ethanol and tetrahydrofuran. The solubility of the isolated 1,4-dibenzothiazole is poor in almost all common solvents, so it was characterized by its C, H, N and S analysis, IR spectrum and melting point. Off-white solid (0.330 mg, 96%), mp 196 °C. FT-IR (KBr, ν/cm^{-1}) 1482 w, 1432 w, 1387 s, 1310w, 1230 w, 970 m, 842 w, 762 m, 724 w, 686 w, 624 w. Anal. Calcd for $C_{20}H_{12}N_2S_2$: C, 69.74; H, 3.51; N, 8.13; S, 18.62. Found: C, 69.80; H, 3.48; N, 8.15; S, 18.60. LC−MS (ESI$^+$): m/z = 345.50, [100%, MH^+]. Calcd for $C_{20}H_{12}N_2S_2$: 345.47.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figure S1, UV−vis spectrum and cyclic voltammogram of the 3,6-diphenyl-1,2,4,5-tetrazine (**phtz**), FT-IR spectra of 2-phenyl-2,3-dihydrobenzothiazole and 2-phenylbenzothiazole, ^{1}H, and ^{13}C NMR spectra (for selected compounds). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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