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Nano ceria catalyzed synthesis of substituted benzimidazole, benzothiazole, and benzoxazole in aqueous media

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ABSTRACT

A series of substituted benzimidazoles, benzothiazoles, and benzoxazoles was synthesized by combining 1,2-phenylenediamine, 2-aminothiophenol, or 2-aminophenol with aryl, heteroaryl, aliphatic, α,β-unsaturated aldehydes in the presence of nano ceria (CeO_2) as an efficient heterogeneous catalyst.

Heteroaromatic bicycles have a wide range of applications in medicinal chemistry because of their pharmaceutical and biological activities.[1] They are the important structural intermediates in the synthesis of variety of pharmaceutical, natural, and agrochemical compounds (Fig. 1). These moieties are the part of compounds showing several biological properties such as anti-hypertensive, anti-ulcer, antiviral, antifungal, anticancer, antihistamine, anti-helminthic, antiparasitic, anticoagulant, antiallergic, analgesic, anti-inflammatory, antimicrobial, and immunosuppressant.[2] The substituted benzimidazoles deliver biological activity against several viruses such as HIV,[3] Herpes (HVS-1),[4] human cytomegalovirus (HCMV),[3] and influenza.[5] Various derivatives of benzothiazoles are also used as radioactive amyloid imaging agents.[6] Benzoxazoles derivatives are isosteres of naturally occurring cyclic nucleotides and they interact with the biopolymers of organisms.[7] These functionalized heterocycles also have various industrial applications.[8] They act as ligands for complexation with transition metals which are used for modeling the biological system in organic reactions.[9]

The broad utility has prompted significant efforts toward the synthesis of these heterocycles. Several methods were reported for the synthesis of these heterocyclic moieties. Synthesis of functionalized 1,2-disubstituted benzimidazoles can be achieved by various routes.[10] The most common route is the direct condensation of 1,2-phenylenediamine with aldehydes. To synthesize this compound, variety of catalysts were used.[11,13] Similarly the substituted benzothiazoles and benzoxazoles were also synthesized by several methods.[12] The most commonly used method to synthesize benzothiazole is the reaction of 2-aminothiophenol with substituted carboxylic acid or aldehydes. Similarly benzoxazole is also synthesized by reacting 2-aminophenol with carboxylic acid or aldehydes.

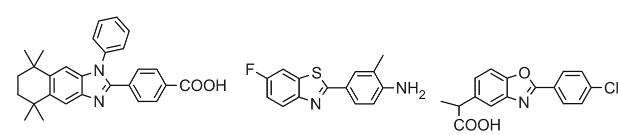

Figure 1. Some benzimidazoles, benzothiazoles, and benzoxazoles.

However, many of these reported methods suffer from one or the other drawbacks such as drastic reaction conditions, long reaction time with poor yield, side products formation, use of toxic reagents and hazardous solvents, use of expensive catalyst, and use of excessive oxidative catalyst. Most of the reported catalysts are homogeneous having no recyclability where as the reactions carried out with heterogeneous catalysts required non green solvents and higher temperatures. Hence a greener route for the synthesis of benzimidazole, benzothiazole, and benzoxazole is needed. Nanometal oxides have higher catalytic activity due to high surface area than their bulk counterparts and due to this they have attracted considerable attention in organic synthesis. However, very few reactions are reported in which nano CeO_2 is used as a catalyst namely transalkylation,[14] Ullmann coupling,[15] and synthesis of α-amino phosphonate.[16a] This indicates that nano ceria is not fully

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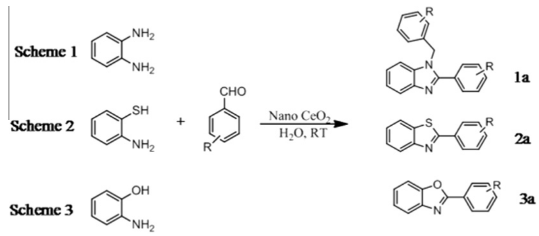


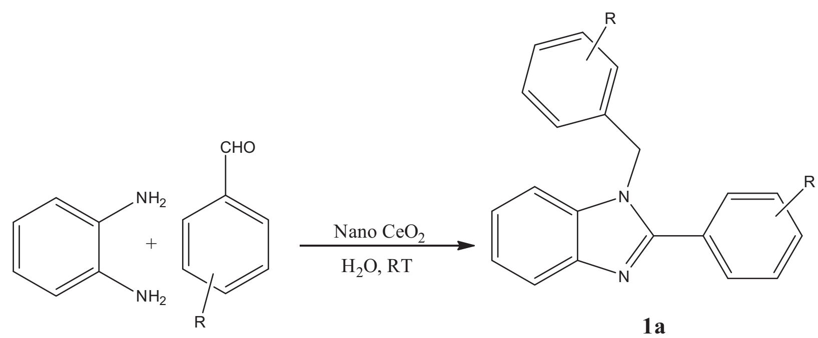
Figure 2. Reaction of 1,2-phenylenediamine, 2-aminothiophenol, and 2-aminophenol with benzaldehyde respectively using CeO_2.

Table 1
Screening of various metal oxides

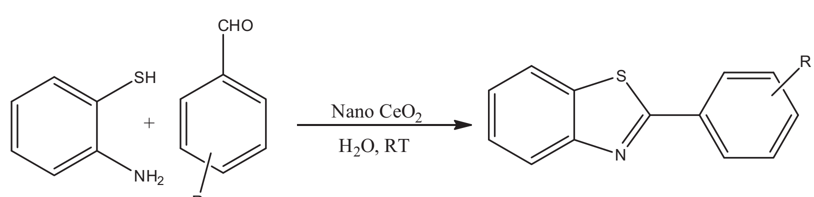
Entry	Metal oxides	Surface area m^2/g	Size	Yield[a] (%)		
				1a	**2a**	**3a**
1	ZnO	12.16	–	54	45	43
2	TiO_2	14.68	–	56	53	48
3	MnO_2	–	22 μm	53	35	31
4	SiO_2	–	60–120 mesh	75	47	45
5	Al_2O_3	–	150–300 mesh	43	61	56
6	La_2O_3	–	14 μm	70	66	68
7	CeO_2	11	–	63	76	64
8	Nano Cu_2O	–	97 nm	44	67	58
9	Nano ZnO	–	50 nm	65	78	77
10	Nano CeO_2	214	4–5 nm	92	96	95

[a] Isolated yield.

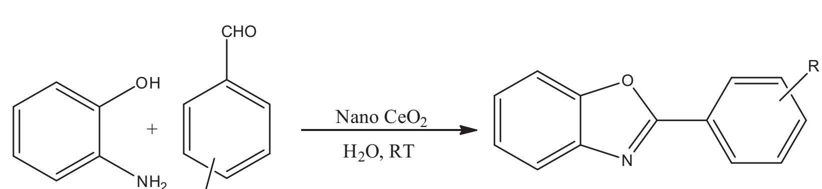
explored for its catalytic activity and hence with this background we have carried out the synthesis of heteroaromatic bicycles in aqueous medium by using nano ceria. Herein we report the condensation of phenylenediamine, 2-aminothiophenol, or 2-aminophenol with aldehydes with the formation of 1,2-disubstituted benzimidazoles, benzothiazoles, or benzoxazoles respectively. Nano CeO_2 showed significant recyclability and activity for these reactions by giving excellent to good product yields. The CeO_2 nano particles are prepared by ultrasonically modified CTAB assisted method.[16b] It is characterized by XRD, SEM, TEM, and EDAX spectra which are given in supporting information. The particle size of nano CeO_2 obtained from TEM analysis is 4–5 nm and the calculated surface area was found to be 214 m^2/g. The reactions were carried out at room temperature and with water as solvent which are the important considerations of greener route of synthesis in organic chemistry. As shown in Figure 2, the reactions of 1,2-phenylenediamine with 2 mol of benzaldehyde (Scheme 1), 2-aminothiophenol with benzaldehyde (Scheme 2), and 2-aminophenol with benzaldehyde (Scheme 3) were selected as model reactions to investigate catalytic activity of nano CeO_2 in aqueous medium at room temperature. To expand the catalytic study, we also



Scheme 1. Synthesis of 1,2-disubstituted benzimidazoles from 1,2-phenylenediamine and substituted benzaldehydes.



Scheme 2. Synthesis of substituted benzothiazoles from 2-aminothiophenol and substituted benzaldehydes.



Scheme 3. Synthesis of 1,2-disubstituted benzoxazoles from 2-aminophenol and substituted benzaldehydes.

Table 2
Optimization of various parameters for model reactions

Entry	Nano CeO_2 (mol %)	Time (min)	Yield[a] (%)		
			1a	**2a**	**3a**
1	0	20	<20	41	36
2	2	20	67	79	74
3	5	20	88	96	95
4	10	20	89	98	97
5	5	10	79	87	80
6	5	30	92	97	95

[a] Isolated yield.

Table 3
Recyclability of nano CeO_2 in catalyzing the model reactions

Entry	No. of cycles	Yield[a] (%)		
		1a	**2a**	**3a**
1	0	92	96	95
2	1	90	93	91
3	2	86	89	88
4	3	81	87	84

[a] Isolated yield.

screened a variety of catalysts for the model reactions such as ZnO, TiO_2, MnO_2, SiO_2, CeO_2, La_2O_3, Al_2O_3, nano Cu_2O, and nano ZnO and the results are summarized in Table 1. The results clearly indicate that nano CeO_2 is superior to other catalysts due to the smaller particle size and high surface area.

The model reactions were optimized for catalyst concentration and time. The results are shown in Table 2. 5 mol % of nano CeO_2 was sufficient for maximum product yields (Table 2, entry 3). An increment in catalyst concentration more than 5 mol % did not show effective increase in product yields (Table 2, entry 4). The reactions proceeded without catalyst but with lower yields, whereas 2 mol % catalyst loading gave fairly good yields (Table 2, entries 1 and 2). This clearly indicates that in the absence of catalyst, reaction did not work beneficially. We also found out the time required to complete the reaction (Table 2, entries 3, 5, and 6). The required time would be 30, 20, and 20 min to get excellent yield of products for the completion of Schemes 1–3 respectively.

Recyclability of the catalyst is an important task in industrial applications. Therefore reusability of nano CeO_2 was investigated for three cycles (Table 3, entries 1–4). The reaction mixture was diluted with ethyl acetate and subsequently centrifuged to get the catalyst. The obtained nano CeO_2 was then washed with acetone followed by drying in oven at 150 °C for 12 h. The recovered catalyst was then used for the next batch of reactions. It was found that the reactivity of the catalyst decreases marginally for the next cycle (approx 4%).

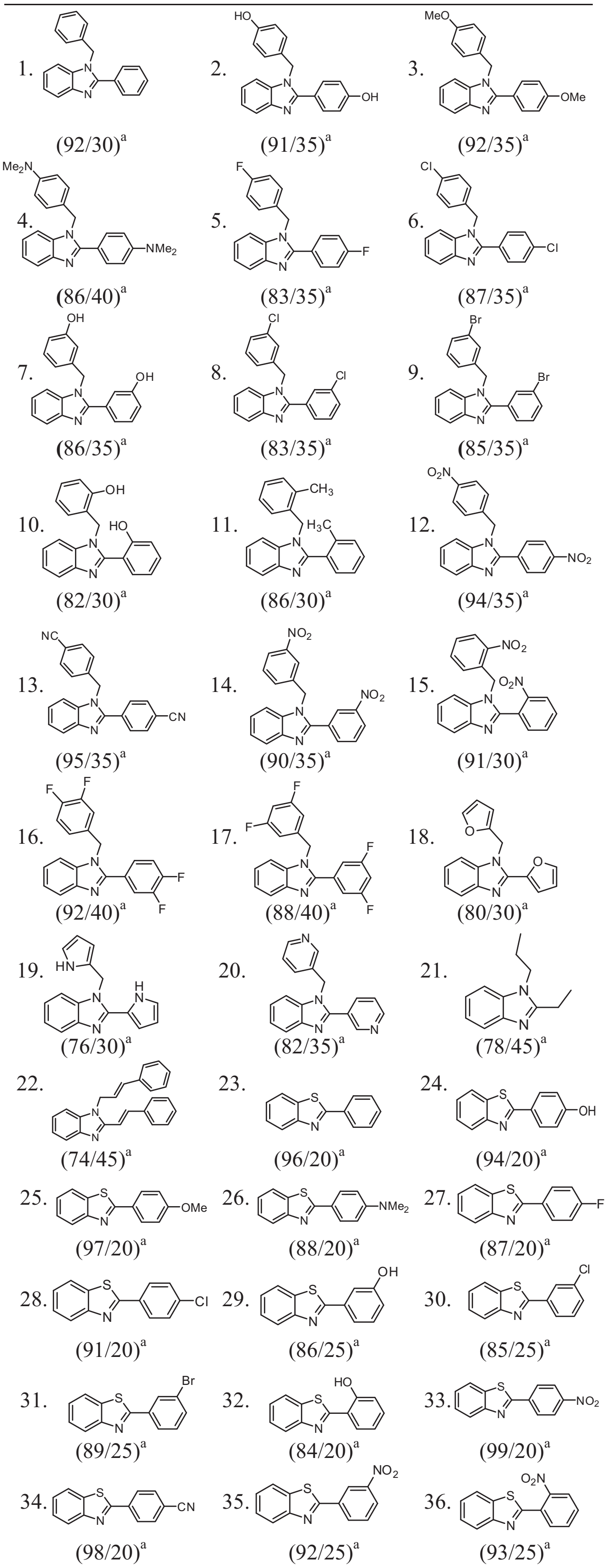
The scope and applicability of the catalyst in the formation of functionalized heterocycles were investigated by using various aromatic, heteroaryl, aliphatic, and α,β-unsaturated aldehydes under the same reaction conditions. The results are summarized in Table 4. In the synthesis of 1,2-disubstituted benzimidazoles, benzothiazoles, and benzoxazoles excellent yield of products have been obtained with aromatic aldehydes. The nature and position of the substituents on the benzene ring of aromatic aldehydes have shown some effect on the yield of the corresponding products. The electron-withdrawing substituents like $–NO_2$ and –CN gave better results than the electron donating substituents such as –OH, $–OCH_3$, $–N(CH_3)_2$, $–CH_3$, –F, –Cl, and –Br. Furthermore the reactivity of these substituent does varies according to their position on the benzene ring of benzaldehyde. The electron-withdrawing substituents gave better product yield at 4 and 2 position of the benzene ring as compared to 3 position (Table 4, entries 12–15, 33–36, and 56–59). While electron-donating ones at these positions gave variable product yields (Table 4, entries 2–11, 24–32, and 47–55). This variation in product yields with nature and position of substituents may be due to resonating, inductive and sterric effects. We also tried aromatic disustituted aldehydes 3,4-difluoro, 3,5-difluoro, 3,4-dimethoxy, and 2-methoxy-5-bromo benzaldehyde and obtained good yield of the corresponding products (Table 4, entries 16, 17, 37–39, and 60–62). The heteroaromatic aldehydes such as furfural aldehyde, pyrrol-2-aldehyde, and pyridine-3-aldehyde have given moderate to good yields of their respective products under similar reaction conditions (Table 4, entries 18–20, 40–42 and 63–65).

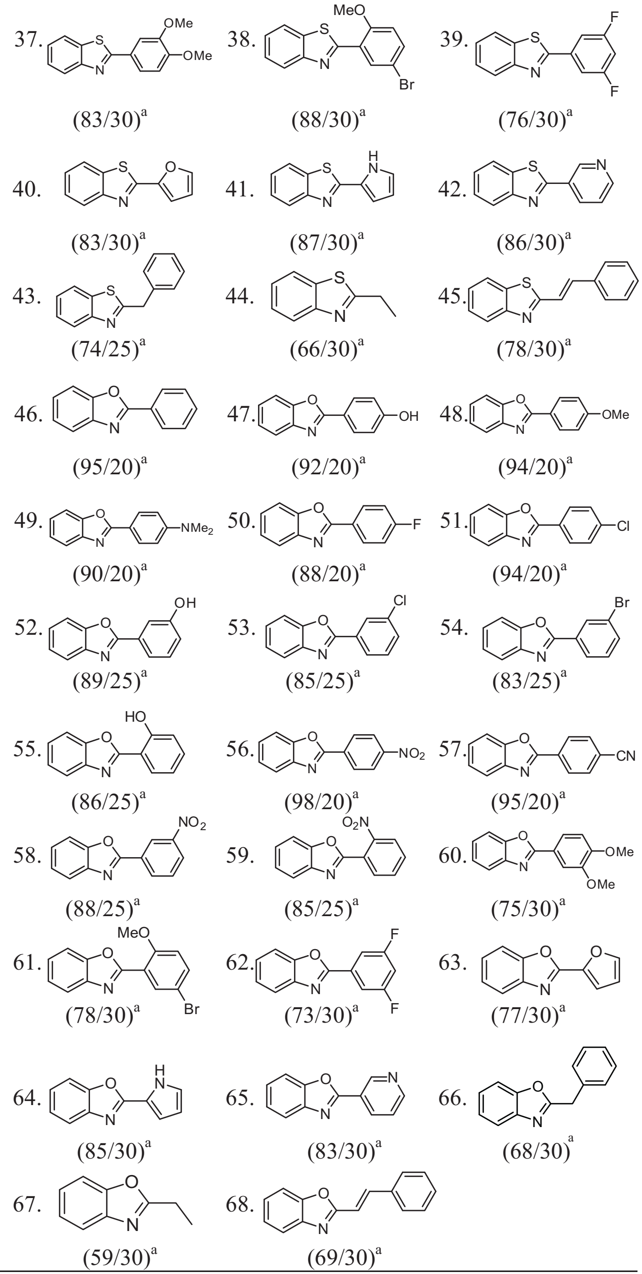
Nano CeO_2 also showed good catalytic activity with aliphatic aldehydes such as propionaldehyde (Table 4, entries 21, 44, and 67). In this substrate study we also screened α,β-unsaturated aromatic aldehydes such as cinnamaldehyde which gave good response to synthesize these heterocycles (Table 4, entries 22, 45, and 68).

In case of Scheme 1, The reaction of 1,2-phenylenediamine and benzaldehyde in 1:2 ratio gave only 1,2-disubstituted benzimidazoles whereas when this ratio was changed to 1:1 then 2-substituted benzimidazole was obtained with 98% product yield under same reaction conditions (Figs. 3–5).

In conclusion, we developed an efficient, selective, and green route by using nano CeO_2 to synthesize variety of 1,2-disubstituted benzimidazoles, 2-substituted benzothiazoles, and 2-substituted benzoxazoles from 1,2-phenylenediamine, 2-aminothiophenol, and 2-aminophenol with aromatic as well as aliphatic aldehydes. All these reactions are feasible at room temperature and in aqueous medium. In case of catalyst concentration, 5 mol % of CeO_2 gave a better yield of products. Aromatic aldehydes have given a

Table 4
Synthesis of benzimidazoles, benzothiazoles, and benzoxazoles using nano CeO_2 in aqueous media





Entry	(Yield/Time)[a]
1.	(92/30)[a]
2.	(91/35)[a]
3.	(92/35)[a]
4.	(86/40)[a]
5.	(83/35)[a]
6.	(87/35)[a]
7.	(86/35)[a]
8.	(83/35)[a]
9.	(85/35)[a]
10.	(82/30)[a]
11.	(86/30)[a]
12.	(94/35)[a]
13.	(95/35)[a]
14.	(90/35)[a]
15.	(91/30)[a]
16.	(92/40)[a]
17.	(88/40)[a]
18.	(80/30)[a]
19.	(76/30)[a]
20.	(82/35)[a]
21.	(78/45)[a]
22.	(74/45)[a]
23.	(96/20)[a]
24.	(94/20)[a]
25.	(97/20)[a]
26.	(88/20)[a]
27.	(87/20)[a]
28.	(91/20)[a]
29.	(86/25)[a]
30.	(85/25)[a]
31.	(89/25)[a]
32.	(84/20)[a]
33.	(99/20)[a]
34.	(98/20)[a]
35.	(92/25)[a]
36.	(93/25)[a]
37.	(83/30)[a]
38.	(88/30)[a]
39.	(76/30)[a]
40.	(83/30)[a]
41.	(87/30)[a]
42.	(86/30)[a]
43.	(74/25)[a]
44.	(66/30)[a]
45.	(78/30)[a]
46.	(95/20)[a]
47.	(92/20)[a]
48.	(94/20)[a]
49.	(90/20)[a]
50.	(88/20)[a]
51.	(94/20)[a]
52.	(89/25)[a]
53.	(85/25)[a]
54.	(83/25)[a]
55.	(86/25)[a]
56.	(98/20)[a]
57.	(95/20)[a]
58.	(88/25)[a]
59.	(85/25)[a]
60.	(75/30)[a]
61.	(78/30)[a]
62.	(73/30)[a]
63.	(77/30)[a]
64.	(85/30)[a]
65.	(83/30)[a]
66.	(68/30)[a]
67.	(59/30)[a]
68.	(69/30)[a]

[a]Isolated yield in %, Time in min.

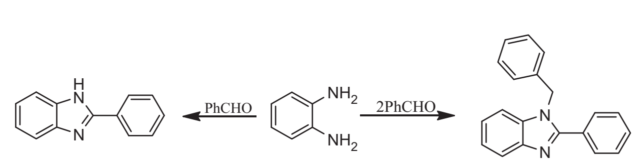


Figure 3. Synthesis of benzimidazole.

better yield of the product than their aliphatic counter parts. The given methodology is efficient, inexpensive, and environmentally benign giving excellent to moderate yields of products. The used catalyst is heterogeneous which is easily separable and recyclable up to three cycles.

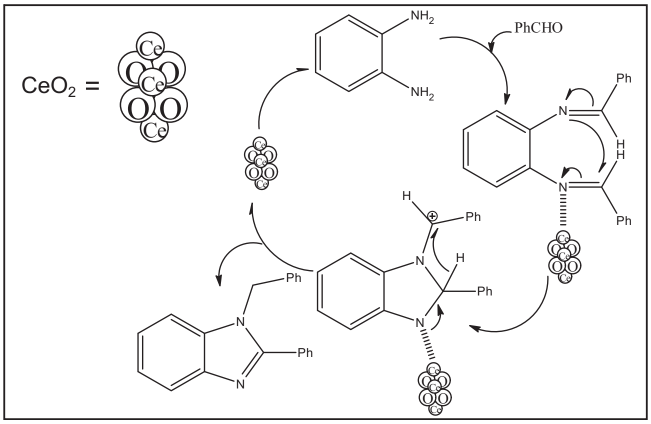


Figure 4. Proposed mechanism for Scheme 1.

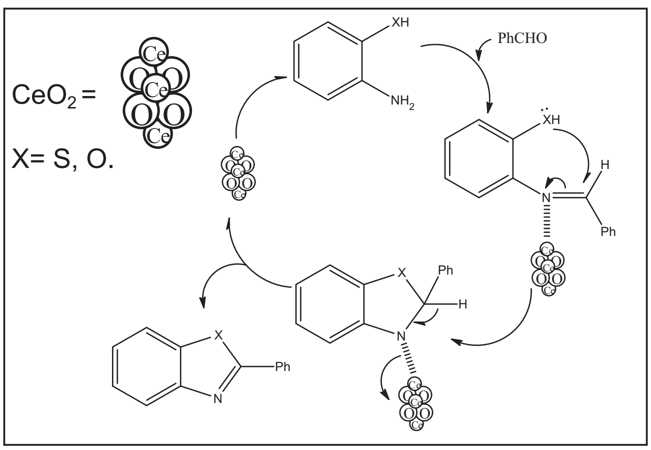


Figure 5. Proposed mechanism for Schemes 2 and 3.

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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.tetlet.2013.09.092.

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