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ORIGINAL PAPER

An efficient synthesis of 2-arylbenzimidazoles from *o*-phenylenediamines and arylaldehydes catalyzed by $Fe/CeO_2–ZrO_2$ nano fine particles

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Abstract 75% $Fe/CeO_2–ZrO_2$ nano fine particles (0.005 mol%) are reported as a new catalyst for the efficient synthesis of 2-arylbenzimidazoles. A simple and convenient procedure, easy purification and shorter reaction times are the advantageous features of this method.

Keywords Benzimidazole · 75% $Fe/CeO_2–ZrO_2$ nano fine particles · Aldehyde · *o*-Phenylenediamine

Introduction

Benzimidazole structural motifs are found in numerous pharmaceutical agents [1, 2] and in materials applications [3–7]. Current clinical examples of benzimidazoles include antihistamines, antiulceratives and topoisomerase inhibitors. The high profile of biological and industrial applications of benzimidazoles has prompted extensive studies of their synthesis. The synthesis of benzimidazoles requires the heating of *o*-phenylenediamine (OPD) and carboxylic acids or their derivatives (nitriles, chlorides, or orthoesters), requires strong acidic conditions, sometimes combined with very high temperatures using polyphosphoric acid or by microwave irradiation [3–10]. Other methods for the synthesis of benzimidazoles involves oxidative cyclodehydration of OPD and aldehydes by using various reagents [11–26]. Although a variety of reagents/catalysts have been recently employed in this second route, unfortunately many of these methods suffer from one or other limitations such as requiring harsh reaction conditions, low to moderate yields, long reaction times, tedious work-up procedures and co-occurrence of several side products. The main disadvantage of most of the existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered and reused. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity, reusability and economic viability. We recently reported a heterogeneous catalyst for the synthesis of heterocyclic compounds [27]. In this communication, we wish to introduce 75% $Fe/CeO_2–ZrO_2$ nano fine particles as a new catalyst for the preparation of 2-arylbenzimidazoles.

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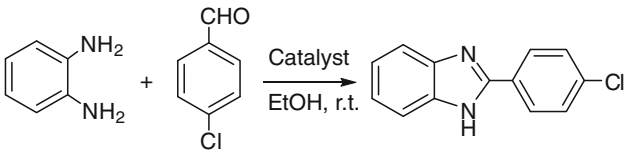
Results and discussion

The main aim of this work was to provide a new catalytic and environmentally benign protocol for the synthesis of 2-arylbenzimidazole derivatives. We hereby report a simple and fast method for the synthesis of 2-arylbenzimidazoles in EtOH using 75% $Fe/CeO_2–ZrO_2$ nano fine particle catalyst at room temperature. In order to establish the optimum conditions for this reaction, various ratios of 75% $Fe/CeO_2–ZrO_2$ nano fine particles were examined using *o*-phenylenediamine and *p*-chlorobenzaldehyde in EtOH at room temperature for 2 h as a model reaction (Scheme 1; Table 1). We observed that very low yields of the desired products were obtained in the absence of 75% $Fe/CeO_2–ZrO_2$ nano fine particles and the best yields were obtained with 75% $Fe/CeO_2–ZrO_2$ nano fine



Scheme 1

Table 1 Effect of the amount of catalyst on the yield of 2-(4-chlorophenyl)benzimidazole

Entry	Catalyst loading (mol%)	Time (h)	Yield (%)[a]
1	No catalyst	2.0	25
2	0.002	2.0	75
3	0.005	2.0	92
4	0.007	2.0	92
5	0.01	2.0	92

[a] Yields refer to isolated products from the reaction of 4-chlorobenzaldehyde (1.0 mmol) and *o*-phenylenediamine (1.0 mmol) in 5 cm^3 ethanol at room temperature

Table 2 Effect of the solvent on the yield of 2-(4-chlorophenyl)benzimidazole

Entry	Solvent	Yield (%)[a]
1	H_2O	80
2	EtOH	92
3	CH_2Cl_2	45
4	MeCN	85
5	Solvent-free	60

[a] All yields refer to isolated products from the reaction of 4-chlorobenzaldehyde (1.0 mmol) and *o*-phenylenediamine (1.0 mmol) in the presence of 75% Fe/CeO_2–ZrO_2 nano fine particles (0.015 g) in 5 cm^3 solvent at room temperature for 2.0 h

particles; thus the catalyst is essential for the synthesis of 2-arylbenzimidazoles.

Next the effect of solvent was examined; different solvents afforded different yields (Table 2).

Obviously, ethanol stands out as the solvent of choice with its fast reaction rate, high yield, selectivity, cheapness and environmental acceptability. In order to evaluate the scope and limitations of this work, we focused our attempts on the synthesis of the benzimidazoles using differently substituted *o*-phenylenediamine and aldehyde derivatives (Scheme 2; Table 3). As can be seen in Table 3 aromatic aldehydes and *o*-phenylenediamine derivatives having different substituents such as methoxy, chloro, nitro and methyl were converted to the corresponding benzimidazoles in high yields. All reactions were carried out within 2 h. Aldehydes containing electron-withdrawing groups gave products in higher yields than those containing electron-donating groups. Fe particles, which are dispersed homogeneously on the surface of the CeO_2–ZrO_2 nano-supported catalyst, act as a Lewis acid and activate the carbonyl group of the aldehyde in the synthesis of the benzimidazole derivatives. The catalyst works under acidic conditions. Protodehalogenation was not observed in any of the reactions studied. Aliphatic aldehydes such as butanal and hexanal were also examined but the yields obtained were low. As can be seen in Scheme 2, two different products, **3** and **4**, are possible for this reaction, but structure **4** was formed in trace amounts.

Conclusions

We have developed a simple, highly efficient, green (due to the use of a heterogeneous, reusable catalyst and inexpensive ethanol as a solvent) and convenient method for the synthesis of biologically important benzimidazole derivatives by the condensation of *o*-phenylenediamine with various aldehyde derivatives at room temperature. This method offers very attractive features such as green synthesis, reduced reaction times and higher yields, all of which make it a useful and attractive strategy for the preparation of various 2-substituted benzimidazole derivatives simply by changing different substrates. The operational simplicity of the procedure is also attractive, which offers wide scope in organic synthesis.

Experimental

Melting points were measured by using the capillary tube method with an Electrothermal 9200 apparatus. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer scanning between 4,000 and 400 cm^{-1}. ^1H NMR spectra were obtained on a Bruker DRX-300 NMR instrument. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on aluminium). All starting materials were purchased from Merck and Acros companies and used without further purification.

Scheme 2

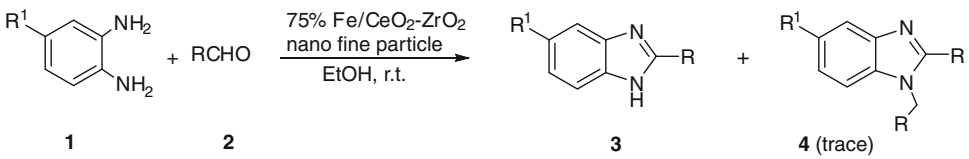


Table 3 Synthesis of benzimidazole derivatives

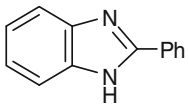
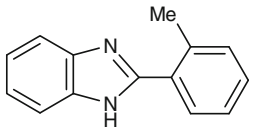
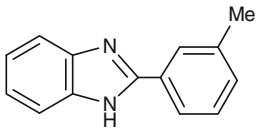
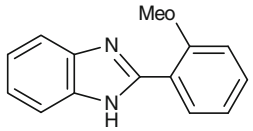
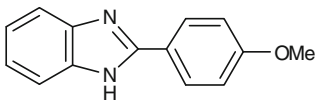
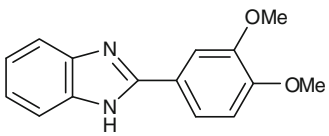
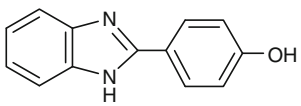
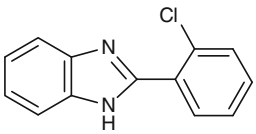
Entry	R^1	RCHO	Product	Yield (%)[a]	M.p. (°C)	
					Found	Reported
1	H	C_6H_5CHO		90	291	290–292 [30]
2	H	2-MeC_6H_4CHO		82	199–202	199–200 [13]
3	H	3-MeC_6H_4CHO		79	214–216	217–219 [31]
4	H	2-$OMeC_6H_4CHO$		84	175–177	178–181 [28]
5	H	4-$OMeC_6H_4CHO$		91	224–226	227–228 [29]
6	H	3,4-$(OMe)_2C_6H_3CHO$		80	234–237	236–238 [32]
7	H	4-OHC_6H_4CHO		85	253–255	254–255 [30]
8	H	2-ClC_6H_4CHO		95	233–235	233–234 [30]

Table 3 continued

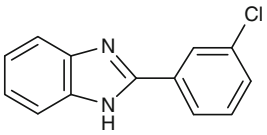
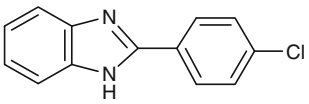
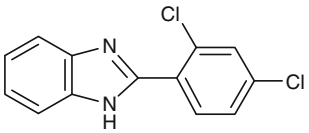
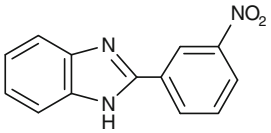
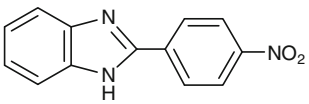
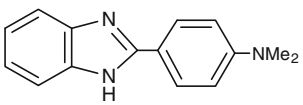
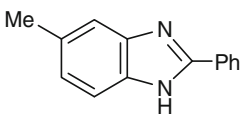
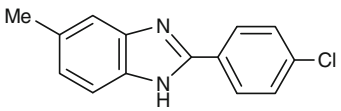
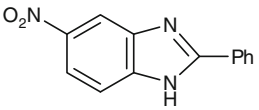
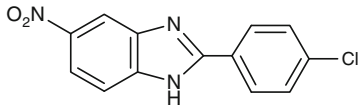
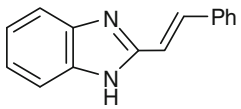
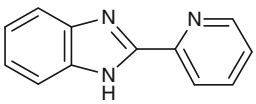
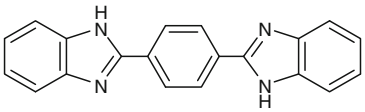
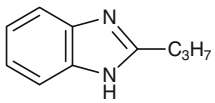
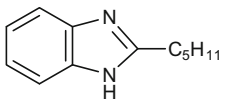
Entry	R^1	RCHO	Product	Yield (%)[a]	M.p. (°C)	
					Found	Reported
9	H	3-ClC_6H_4CHO		90	227–229	230–232 [30]
10	H	4-ClC_6H_4CHO		92	290–291	292–293 [30]
11	H	2,4-$(Cl)_2C_6H_3CHO$		93	226–228	227 [33]
12	H	3-$NO_2C_6H_4CHO$		88	205–207	204–207 [28]
13	H	4-$NO_2C_6H_4CHO$		91	310–312	311–312 [29]
14	H	4-$(Me)_2N$ C_6H_4CHO		88	261–263	264–266 [34]
15	CH_3	C_6H_5CHO		89	240	242–243 [13]
16	CH_3	4-ClC_6H_4CHO		90	225–228	224–225 [13]
17	NO_2	C_6H_5CHO		82	205–207	206–209 [35]

Table 3 continued

Entry	R^1	RCHO	Product	Yield (%)[a]	M.p. (°C)	
					Found	Reported
18	NO_2	4-ClC_6H_4CHO		80	275–278	277–281 [36]
19	H	*trans*-$C_6H_5CH{=}CHCHO$		88	201–202	199–202 [34]
20	H	2-Pyridinecarbaldehyde		84	216–219	218 [30]
21	H	1,4-Benzenedicarbaldehyde		80	>300	>300 [37]
22	H	*n*-C_3H_7CHO		Trace	–	–
23	H	*n*-$C_5H_{11}CHO$		Trace	–	–

[a] All yields refer to GC analysis

Synthesis of 75% Fe/CeO_2–ZrO_2 nano fine catalyst by co-precipitation method

$Ce(NO_3)_3{\cdot}6H_2O$ (0.2 mol), 0.8 mol $ZrOCl_2{\cdot}8H_2O$, and 2.0 g of mineral clay containing of 75% $FeCl_2{\cdot}4H_2O$ (w/w) were dissolved in a mixture of distilled water, isopropanol, and Tylose (hydroxylethyl cellulose) as a dispersant, and the resulting solution was transferred to a round-bottom flask. To this solution, an aqueous solution of 20% KOH (w/w) was added dropwise at 80 °C with constant stirring to attain pH 9 at 80 °C. The precipitate was thoroughly washed with distilled water several times to remove any potassium impurity and then initially air-dried for 48 h, followed by drying at 100–120 °C for 6 h. This material was finally calcined at 800–850 °C in an aerobic environment to get the final nanocatalyst.

Typical procedure for preparation of 2-arylbenzimidazoles

For each reaction, a mixture of *o*-phenylenediamine **1** (1.0 mmol) and aldehyde **2** (1.0 mmol) was stirred in 5 cm^3 of 96% EtOH in the presence of 0.015 g catalyst at room temperature for 2 h. Progress of the reaction was monitored by TLC using *n*-hexane/ethyl acetate (8:1). After the reaction was completed, 10 cm^3 hot EtOH was added, the catalyst was filtered off and then 30 cm^3 ice-water was poured into the filtrate. The solid product was

Table 4 Reusability of the catalyst in the model reaction

Entry	Cycle	RCHO	Yield (%)
1	Fresh	4-Chlorobenzaldehyde	92
2	1st	4-Chlorobenzaldehyde	92
3	2nd	4-Chlorobenzaldehyde	89
4	3rd	4-Chlorobenzaldehyde	87

filtered, washed with *n*-hexane and subsequently dried. The corresponding benzimidazole was obtained as the only product (Table 3, Scheme 2). An identical procedure was employed using *o*-phenylenediamine (2.0 mmol) and terephthalaldehyde (1.0 mmol) stirred in 5 cm^3 of 96% EtOH in the presence of 0.030 g catalyst at room temperature for 2 h for the synthesis of bis-benzimidazoles. All the benzimidazoles produced were characterized in detail by IR and ^1H NMR spectroscopy and these data were compared with those reported in the literature.

Recyclability of the catalyst

The reusability of the catalyst was also studied. At the end of the reaction, the catalyst was removed by filtration and washed with diethyl ether. The recycled catalyst could be subjected to further reactions. In the case of the model reaction, after four runs the catalytic activity of catalyst was almost the same as that of the freshly used catalyst (Table 4).

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