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Research Article

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"An efficient synthesis of Benzimidazole by cyclization–oxidation processes using Fe/MgO as a heterogeneous recyclable catalyst"

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ABSTRACT

A convenient and straightforward method has been developed for the synthesis of benzimidazole using aryl aldehydes and o-phenylene diamine in the presence of Fe containing Magnesium oxide (Fe/MgO), at room temperature. The salient feature of this method includes mild condition, short reaction time, high yield, easy purification, recyclable catalyst, large scale synthesis and simple procedure. The catalyst can be reused for several cycles without decrease in activity.

Keywords Benzimidazole, Fe/MgO, Recyclable catalyst, Room temperature.

INTRODUCTION

Benzimidazoles and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities and these are well-documented in literature. They show selective neuropeptides YY, receptor antagonists [1], potent inhibitors of TiE-2 and VEGFER_2 tyrosine kinase receptor [2], gamma-amino butyric acid (GABA) agonists and 5-HT3 antagonists [3]. They have been showing promising activities in the treatment of several diseases like epilepsy, diabetes, and antifertility [4]. For these reasons, they gained much attention as important pharmacophore and privileged structure in medicinal chemistry [5] encompassing a diverse range of biological activities [6]. These benzimidazoles derivatives have found commercial application in veterinarian medicine as anthelmintic agents and diverse human therapeutic areas [7]. Realizing the importance of these compounds, numerous methods have been reported in the literature for the synthesis of benzimidazoles like condensation reaction of 1,2-phenylenediamine with carboxyaldehydes, carboxylic acids or their derivatives [8,9] such as chlorides, nitriles and orthoesters, under strong acidic conditions with high temperatures. This benzimidazoles are also synthesized by the condensation of o-aryldiamines and aldehydes in refluxing nitrobenzene [10]. The condensation of o-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid [11] or mineral acids [12]. Direct condensation of *o*-aryldiamines and aldehydes are not a good synthetic reactions, as it is well known to yield a complex mixture, being 1,2-disubstituted benzimidazoles. In this case, however, the addition of transition metal, namely dipyridine copper (II) chloride [13]. Copper acetate, [14] or lead tetracetate [15] allows a partial selective synthesis of benzimidazoles. In recent years, solvent-free synthesis of benzimidazoles under microwave irradiation using $Yb(OTf)_3$, [16] MoO_3/CeO_2-ZrO_2,[17] metal halide supported alumina [18] and $SbCl_3$–Al_2O_3 [19] have been reported. But some of these processes have certain limitations, such as harsh reaction conditions, tedious work up procedures, long reaction times, low yields and co-occurrence of several side reactions.

Recently, many metal oxides based catalytic systems are widely used in variety of organic reactions like cyclization oxidation reaction [20,21]. Though, those based catalyst are used in number of reactions, these reactions takes place over a longer period, gives low yield and forms byproducts [22]. These limitations can be overcome by using metal containing metal oxide, X-Meng et.al [23] have reported catalytic oxidation by molecular oxygen catalyzed Ni-TiO_2, the similar catalyst like SO_4/ZrO_2,[24] Li/MgO,[25] CeO/CoO [26] etc. now used for a variety of enantioselective reaction such as Knovendgel reaction and oxidation reaction.

With this in mind, in the present study, we report the synthesis of benzimidazoles from aldehydes and o-phenylene diamines using Fe/MgO nanocrystalline catalyst (Scheme 1). They have been successfully utilized in several organic transformations to minimize undesirable waste causing environmental pollution [27]. It has been received more attention due to its high thermal stability, large specific surface area, easy recovery and good ability to perform organic reactions at lower temperatures.

EXPERIMENTAL SECTION

All Chemicals were employed are commercial products (Aldrich Chemical Co) and were used without purification. All yields refer to isolated products after purification. ^{1}H (300 MHz) NMR and ^{13}C (75 MHz) NMR spectra were recorded on Varian mercury XL-300 and Bruker spectrometer instruments using TMS as internal standard. The solvent used for NMR spectra was $CDCl_3$ and DMSO-d_6. Infra red spectra were taken on Shimadzu FTIR–408 in KBr. The mass spectra were recorded on Shimadzu GC-MS QP 2010A mass spectrometer with an ionization potential of 70 eV. Column chromatography was performed on silica gel (230–400 mesh) supplied by Acme Chemical Co.

General Procedure

In a typical run, o-phenylene diamines (1.1 mol), aryl aldehydes (1.3 mol) and Fe/MgO (0.8 mol) nanoparticles were allowed to react in methanol at room temperature for 25 min. The reaction mixture was directly filtered and washed with methanol. The recovered catalyst was dried and reused further in successive reactions. Filtrate was collected and evaporated under reduced pressure to afford the product. The products obtained were confirmed by IR, NMR and Mass spectrometry.

Spectral data of selected compounds

2-Phenyl-1H-benzimidazole (1): FT-IR (KBr): 3500, 1718, 1600, 948, 740 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.20 - 8.20 (m, 4H), 7.46-7.62 (m, 5H), 12.02 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 115.16, 139.17, 129.97, 129.06, 128.88, 126.50, 122.16, 151.03 ; Mass m/z: 195 (M+1).

2-(4-chlorophenyl)-1H-benzimidazole (10): FT-IR (KBr): 3548, 1722, 1600, 1450, 1550, 748 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.21-8.18 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4, 2H), 12.94 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 115.53, 119.06, 121.90, 122.67, 126.74, 127.81, 129.86, 135.30, 139.90, 144.82, 152.73; Mass m/z: 229 (M+1).

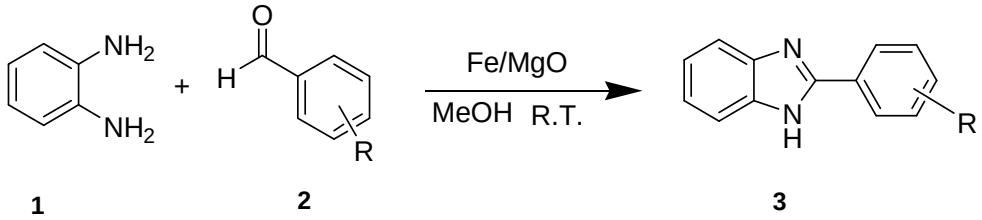
2-(4-methoxyphenyl)-1H-benzimidazole (7): FT-IR (KBr): 3544, 1724, 1610, 1450, 1100, 1200, 950 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 3.83 (s, 3H, CH_3), 7.09 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.20 - 8.12 (m, 4H), 11.65 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.12, 110.39, 114.28, 118.42, 121.35, 121.97, 122.67, 127.93, 134.92, 143.84, 151.28, 160.54; Mass m/z: 225 (M+1).

2-Styril-1H-benzimidazole (13): FT-IR (KBr): 3545, 1710, 1640, 1550, 948, 750 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 7.09 (d, *J* = 16 Hz, 1H), 7.24-7.30 (m, 2H), 7.33 (m, 2H), 7.38 (m, 2H), 7.57 (m, 2H), 7.70 (m, 1H), 7.76 (d, *J* = 16 Hz, 1H), 12.92 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 110.28, 113.97, 119.86, 124.47, 128.16, 127.53, 128.93, 129.72, 135.17, 139.43, 142.21, 150.43, 162.77; Mass m/z: 221 (M+1).

RESULTS AND DISCUSSION

For our investigation, Fe/MgO was prepared according to the literature procedure [28]. In order to determine the most appropriate reaction conditions and evaluate the catalytic efficiency of Fe/MgO catalyst for the synthesis of benzimidazoles; initially a model study was carried out on the synthesis of benzimidazole (Scheme 1) using p-chloro

benzaldehyde as a model substrate. The reaction was monitored by TLC technique using ethyl acetate-hexane (3:7 v/v) as a solvent system.



Scheme 1 Synthesis of benzimidazoles

To evaluate and optimize the effectiveness of Fe/MgO with different catalyst, we tried MgO, Co/MgO and Cu/MgO for the cyclization reaction of o-phenylene diamine and p-chloro benzaldehyde. MgO gave poor yield while Cu and Co/MgO gave good yield but required more time as compared to Fe/MgO (Table **1**).

Table 1. Effect of different metal on reaction time and yield

Sr.no.	Catalyst	Time (min)	Yield*
1.	MgO	90	34
2.	3% Fe/MgO	67	79
3.	7% Fe/MgO	26	94
4.	10% Fe/MgO	30	89
5.	Cu/MgO	50	91
6.	Co/MgO	40	79

With increasing Fe loading from 0 to 10%, cyclization substantially increases and it reaches a maximum (94%) at the Fe content of 7%. Further, increasing Fe content, however, lowers the cyclization rate. As evidenced by XRD, Fe species loading lower than 10%, whereas high Fe contents (>10%) results in microcrystalline phase, Fe located outside the internal channels, resulting in a remarkably poor catalytic activity. Therefore, it shows that a moderate incorporation of Fe results in higher catalytic activity. Thus, it is obvious from our studies that 7% Fe/MgO was superior in the cyclization reaction with good yield in short time. To optimize the amount of catalyst required for the cyclization we tried various mol equivalents of the catalyst compared to the quantity of the phenylene diamine (Table **2**). It was found that when reaction was carried out with 0.8 mol equivalents cyclization was 94%.

Table 2. Effect of mole percentage of Fe/MgO

Sr.no.	(mol) of Fe/MgO	Time (min)	Yield*
1.	0.1 mol	80	78
2.	0.4 mol	40	89
3.	0.8 mol	26	94
4.	1.2 mol	25	87

When the cyclization reaction was carried out in different solvents such as DMF, methanol, ethanol, acetonitrile, dichloromethane and the result clearly showed that methanol was found to be the best choice (Table **3**).

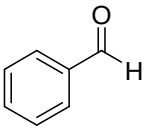
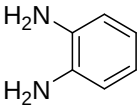
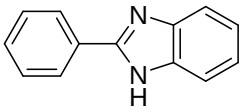
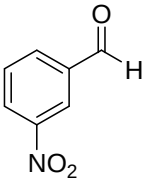
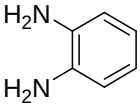
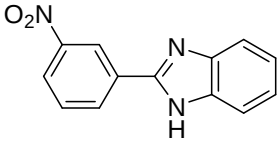
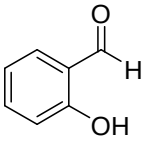
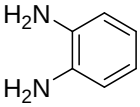
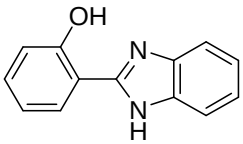
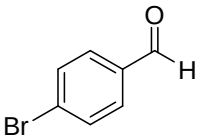
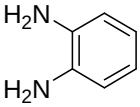
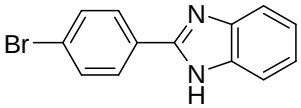
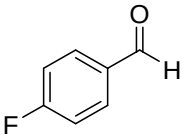
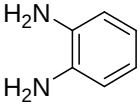
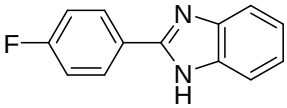
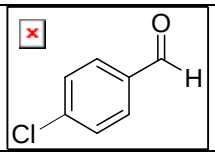
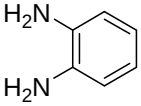
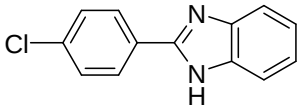
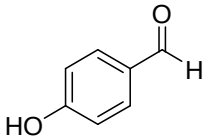
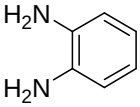
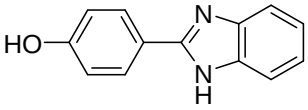
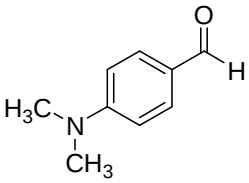
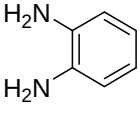
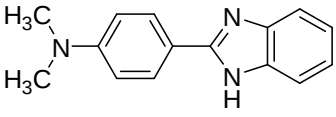
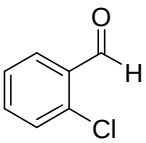
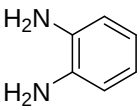
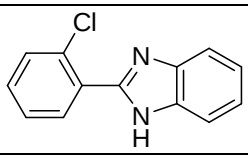
Table 3. Effect of Solvent for benzimidazoles using Fe/MgO

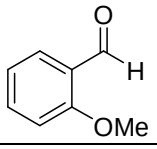
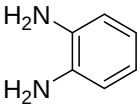
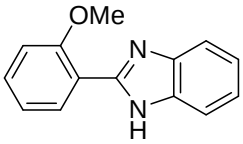
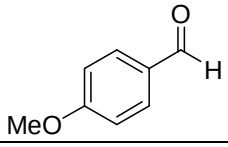
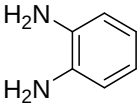
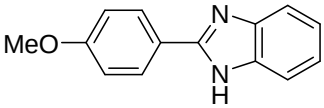
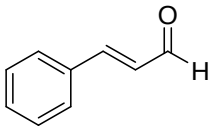
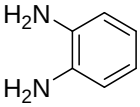
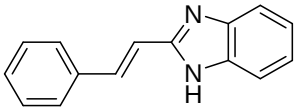
Sr. no.	Solvent	Time	Yield*
1.	MeOH	25	94
2.	EtOH	25	91
3.	DMF	45	86
4.	CH_3CN	40	89
5.	CH_2Cl_2	60	69

In order to evaluate the generality of the process, several diversified examples illustrating the present method for the synthesis of benzimidazoles was studied (Table **4**). The cyclization reaction o-phenylene diamine was checked by treating with wide range of substituted aldehydes bearing electron donating (such as hydroxy, methoxy, methyl, N,N-dimethyl) or electron withdrawing (nitro, halides) was carried out in the presence of Fe/MgO catalyst. The

reaction of aromatic aldehydes with electron donating groups reacted very well at faster rate compared to electron withdrawing groups. Treatment of substituted aldehydes with o-phenylene diamine in methanol with 7% Fe incorporated MgO (0.8 mol) at room temperature afforded benzimidazole with excellent yield. The results obtained are illustrated in table 4. All the products obtained were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy.

Table 4. Synthesis of benzimidazoles in the presence of Fe/MgO nanoparticle

Entry	Aldehyde	1,2-Diamine	Time (min)	Product	Isolated Yield (%)
1.			25		92
2.			50		96
3.			40		89
4.			26		92
5.			24		87
6.			30		94
7.			30		86
8.			20		90
9.			37		89

10.			28		91
11.			40		87
12.			50		84

The reusability of the catalyst was tested in the synthesis of benzimidazoles as shown in table **5**. The catalyst was recovered after each successive run, washed three times with acetone, dried in oven at 120 ^{0}C for 3 hrs. Prior to use and tested for its activity in the subsequent run. The catalyst was tested for 5 runs. It was observed that the catalyst displayed very good reusability.

Table 5. Results of the reaction run in the presence of recycled catalyst

Sr. no	Reaction run	time	Yield*
1.	1	25	94
2.	2	25	94
3.	3	25	92
4.	4	25	87
5.	5	25	90

**All reactions (Table.1-4) are carried at room temperature using Fe/MgO.*

CONCLUSION

In conclusion, we developed an efficient and simple alternative for the preparation of benzimidazole using Fe/MgO catalyst at room temperature. Prominent among the advantages of this new method are simple procedure, easy workup procedure, short reaction time and good yield and also use of cheap, nontoxic and easily synthesized Fe/MgO catalyst.

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