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EFFICIENT SYNTHESIS OF BENZIMIDAZOLE AND QUINOXALINE DERIVATIVES WITH $ZnO.H_2O_2$ UNDER MILD CONDITIONS

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ABSTRACT

Various benzimidazoles and quinoxalines derivatives have been synthesized with excellent yields using a catalytic amount of zinc oxide with hydrogen peroxide ($ZnO.H_2O_2$) at room temperature. The advantages of this synthetic protocol are a wide substrate range, easy handling and commercially available inexpensive catalyst.

Key words: Benzimidazoles, Quinoxalines, Zinc oxide, Hydrogen peroxide.

INTRODUCTION

The development of simple, efficient, environmentally-benign and economically viable chemical processes or methodologies for widely used organic compounds is in great demand.[1] Benzimidazole are present in various bioactive compounds possessing antiviral, antihypertension and anticancer properties.[2,3] Compounds possessing the benzimidazole moiety express significant activity against several viruses such as HIV,[4] Herpes(HSV-1)[5] and influenza[6]. Bis-benzimidazole is DNA-minor grove binding agents possessing anti-tumour activity.[7]

The condensation of o-phenylenediamine with carbonyl compounds in the presence of strong acids such as polyphosphoric acid or mineral acids[8] and other reagents such as $I_2/KI/K_2CO_3$,[9] N-halosuccinamide (X = Cl, Br, I),[10] $Yb(OTf)_3$,[11], PEG-100,[12], $(NH_4)\ H_2\ PW_{12}\ O_{40}$,[13] and palladium as well as microwave irradiation[14] and solid phase reactions,[15] are reported in literature. However, many of the synthetic protocols reported so far suffer from disadvantages, such as the requirement for anhydrous conditions, use of organic solvents,

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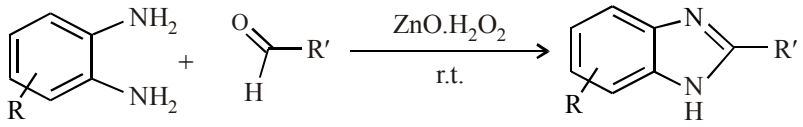
harsh reaction conditions, prolonged reaction times, expensive reagents and low to moderate yields.

EXPERIMENTAL

Almost all the reported methods make use of an acid catalyst, giving rise to tedious working procedures. Therefore, the development of a cost-effective, safe and environmentally friendly reagent is still needed.



R: H, Alkyl
R': Alkyl, Aryl

Scheme 1

In this communication, we report a simple and efficient method for synthesis of benzimidazole and quinoxaline derivatives using zinc oxide and hydrogen peroxide as a catalyst under mild conditions.

Typical experimental procedure for synthesis of benzimidazole derivatives

A mixture of o-phenylenediamine (2 m mol), p-nitrobenzaldehyde (2 m mol) and zinc oxide-hydrogen peroxide (0.1 m mol : 1 mL) was stirred magnetically at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered and extracted with ethyl acetates (3 x 30 mL). The combined ethyl acetates extracts were dried with Na_2SO_4 and concentrated under reduced pressure. In all the cases, the products obtained after the usual work up gave satisfactory spectral data.

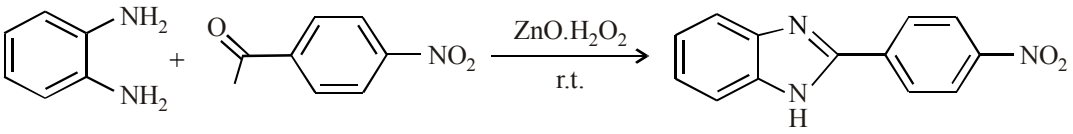
Typical experimental procedure for synthesis of quinoxaline derivatives

A mixture of o-phenylenediamine (2 m mol), benzil (2 m mol) and zinc oxide-hydrogen peroxide (0.1 m mol : 1 mL) was stirred magnetically at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered and extracted with ethyl acetates (3 x 30 mL). The combined ethyl acetates extracts were dried with Na_2SO_4 and concentrated under reduced pressure. In all the cases, the products obtained after the usual work up gave satisfactory spectral data.

RESULTS AND DISCUSSION

The catalytic activity of zinc oxide for the benzimidazoles derivatives of o-phenylenediamine (2 m mol) and p-nitrobenzaldehyde (2 mmol) under room temperature was studied and it was found that the application of less than 0.1 mmol of zinc oxide in hydrogen peroxide (1 mL) gave a moderate yield of the benzimidazoles (Table 1, entries-**1, 2, 3**), whereas the use of more than 0.1 m mol gave an excellent yield (Table 1, entries-**4, 5, 6**).

Table 1: Catalytic effect of ZnO on o-phenylenediamine (2 m mole) and p-nitrobenzaldehyde (2 m mol) in the presence of hydrogen peroxide (1 mL) at room temperature



Entry	ZnO mmol (mg)	Time (min)	Yield (%)[a]
1.	0.005 (0.4)	60	65
2.	0.01 (0.8)	50	70
3.	0.05 (4)	40	78
4.	0.10 (8)	20	96
5.	0.15 (12)	20	96
6.	0.20 (16)	20	96

In order to find out the most effective catalyst for preparation of benzimidazole derivatives, we employed various metal oxides during the benzimidazole formation from o-phenylenediamine and p-nitrobenzaldehyde (2 : 2m mol) in the presence of hydrogen peroxide (1 mL) at room temperature. (Table 2).

According to the results obtained, zinc oxide was found to be the most efficient catalyst (Table 2, entry-**2**). However, other metal oxides such as CuO, MgO, Cu_2O_3 and CaO exhibit less significant catalytic properties in the formation of benzimidazole derivatives.

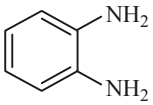
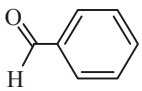
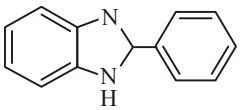
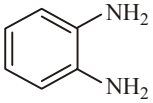
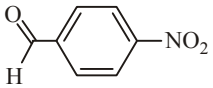
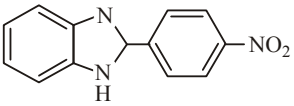
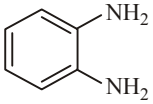
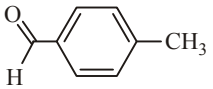
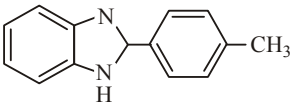
Table 2: Synthesis of benzimidazole in the presence of different metal oxides, at room temperature

Entry	Metal oxide	mmol (mg)	Time (min)	Yield (%)
1.	CuO	0.1 (8)	40	85
2.	ZnO	0.1 (8.1)	20	96
3.	MgO	0.2 (8)	45	45
4.	Cu_2O_3	0.1 (17.6)	50	44
5.	CaO	0.1 (5.6)	60	30

[a]Isolated yields

We used a wide variety of compounds, to which was applied optimal reaction conditions, to prepare a wide range of benzimidazoles. The results are summarized in Table 3. Variety of aldehydes (aliphatic, heterocyclic and aromatic) possessing both electron-donating and electron withdrawing groups were employed for benzimidazole formation and in all cases, the yields were excellent. (Table 3, entries **1-18**). Four different types of o-phenylenediamines were employed and all of them reacted smoothly under the reaction conditions. The aliphatic aldehydes, which were also reacted under similar conditions, gave considerable yields (Table 3, entries **12-13**). All the known products were characterized by compairing their physical and spectral (IR, NMR) data with authentic samples reported in the literature.

Table 3: Synthesis of benzimidazole in presence of $ZnO.H_2O_2$ at room temperature

Entry	1, 2-Diamine (a)	Aldehyde	Product (b)	Time (min)	Yield (%)
1.				20	95
2.				20	96
3.				20	94

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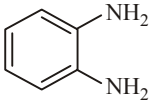
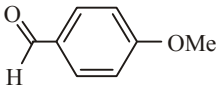
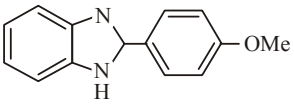
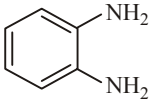
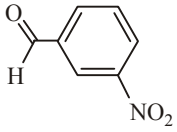
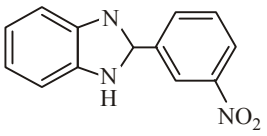
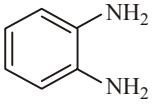
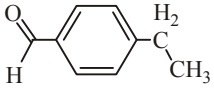
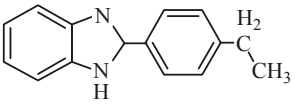
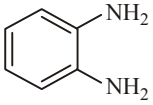
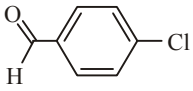
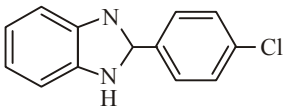
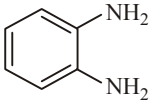
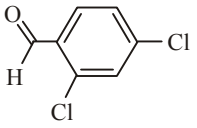
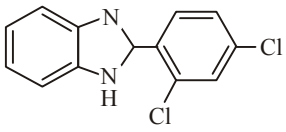
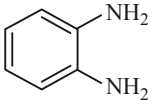
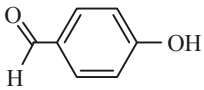
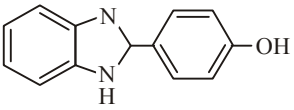
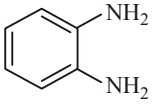
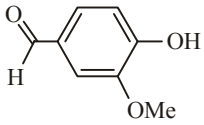
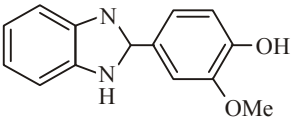
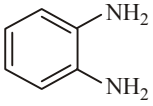
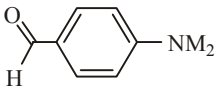
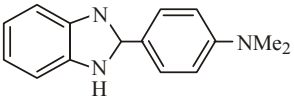
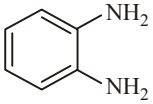
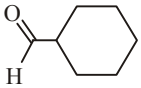
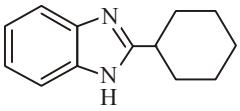
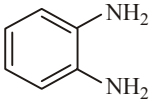
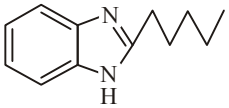
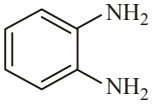
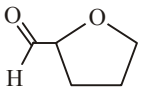
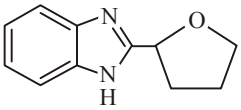
4.				20	90
5.				20	92
6.				20	92
7.				20	89
8.				30	90
9.				30	87
10.				40	85
11.				40	91
12.				60	88
13.				60	85
14.				60	87

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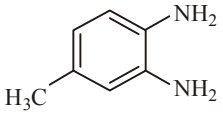
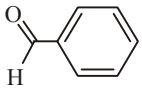
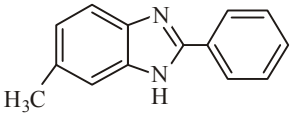
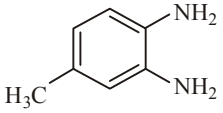
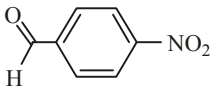
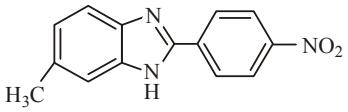
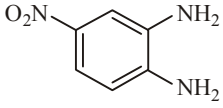
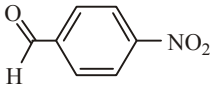
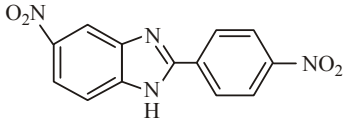
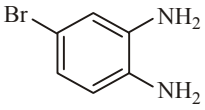
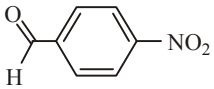
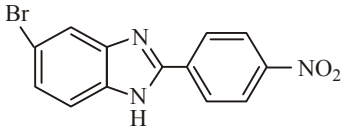
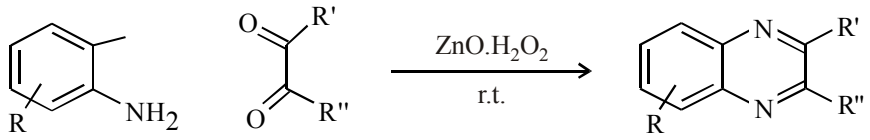
Entry	1, 2-Diamine (a)	Aldehyde	Product (b)	Time (min)	Yield (%)
15.				20	96
16.				20	94
17.				10	96
18.				20	92

[a] The substrate was treated with benzaldehyde (2 mmol) by using 0.1 mmol of ZnO in the presence of H_2O_2 under neat conditions at room temperature.
[b] All products were identified by their IR and ^{1}H NMR spectra
[c] Isolated yields.

Quinoxaline derivatives are an impotant class of nitrogen containing heterocycles and they constitute useful intermediates in organic synthesis. Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities such as antibacterial, anti-inflammatory, antiviral and anticancer activity.[16] Besides these, their applications in dyes,[17] efficient electroluminescent materials,[18] organic semiconductors,[19] building blocks for the synthesis of anion receptor,[20] cavitands,[21] dehydroannulenes[22] and DNA cleaving agents[23] have been reported. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.

Over the years, numerous synthetic methods for preparation of quinoxalines have been reported in the literature.[24] Among them, the condensation of 1,2-aryldiamine with 1,2-diketone in refluxing ethanol or acetic acid is a general approach.[25] Research efforts have been focused on finding new catalysts to improve the yield of this condensation reaction. In addition to common Lewis acids, many other catalysts including I_2,[26a,26b] SA,[26c] Montmorilinite K-10,[26d] SSA,[26e] $H_6P_2W_{18}O_{62}$. $24H_2O$,[26f] $InCl_3$,[26g] $MnCl_2$,[26h] $CuSO_4.5H_2O$,[26i] CAN,[26j], p-TsOH[27], Ga(OTF)3[28] and microwave[29] have been reported. Herein, we report a simple, highly efficient process for the preparation of the biologically important quinoxaline

derivatives through the reaction of 1,2-diamines and 1,2-diketones by using zinc oxide and hydrogen peroxide as a catalyst (**Scheme 2**).

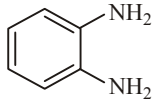
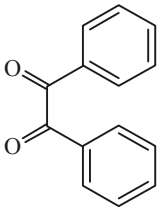
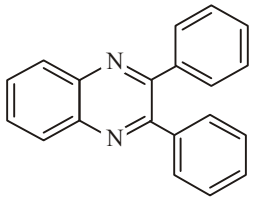
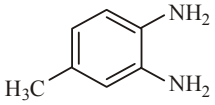
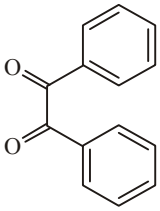
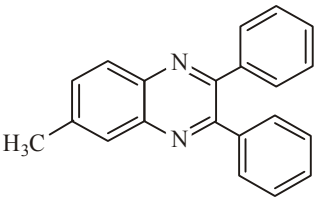


R, R = alkyl, aryl
R = H, alkyl

Scheme 2

In order to expand the scope of this new protocol to synthesize quinoxaline from o-phenylenediamine and diketones, we investigated the reaction in the presence of zinc oxide with hydrogen peroxide (Table 4, entries **1-16**). Results in Table 4 show that electron-donating groups at the phenyl ring of 1, 2-diamine favored the product with quantitative yields (Table 4, entries **2, 7** and **10**). In contrast, electron-withdrawing groups such as nitro, chloro and bromo groups afforded slightly lower yields. Ethylene- 1, 2-diamine,which were also reacted under similar conditions, gave considerable yields (Table 4, entries **13-15**). Different 1, 2-diketones gave excellent yields of quinoxaline derivatives, while 1,2-dialkylketones afforded the reaction Table 4, entries **16**).

Table 4: **Synthesis of quinoxaline in presence of $ZnO.H_2O_2$ at room temperature**

Entry	1, 2-Diamine (a)	1,2 Diketone	Product (b)	Time (min)	Yield (%)
1.				10	98
2.				10	99

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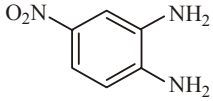
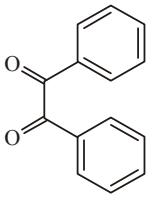
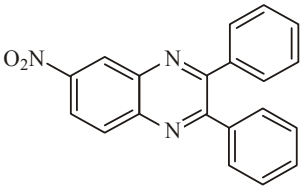
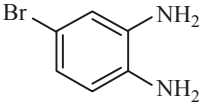
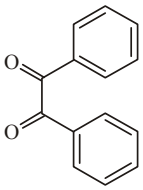
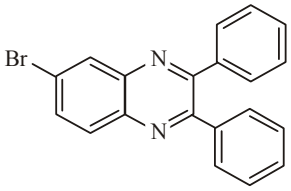
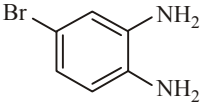
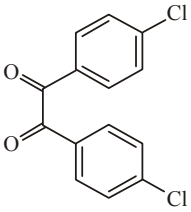
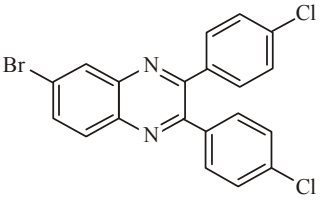
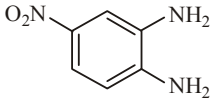
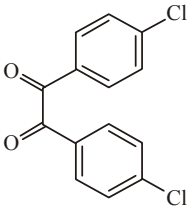
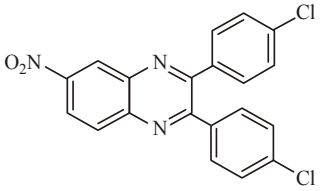
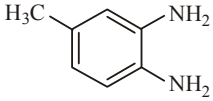
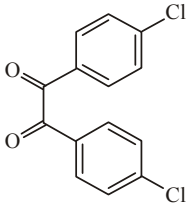
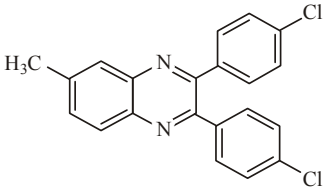
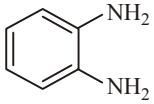
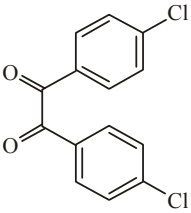
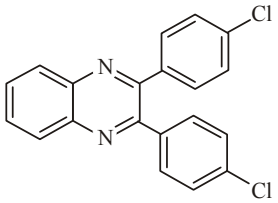
Entry	1, 2-Diamine (a)	1,2 Diketone	Product (b)	Time (min)	Yield (%)
3.				10	90
4.				10	89
5.				10	90
6.				10	91
7.				5	96
8.				10	98

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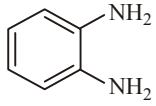
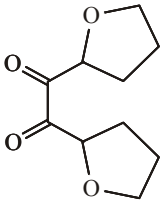
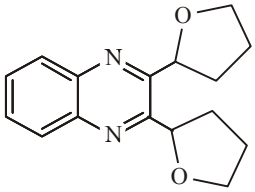
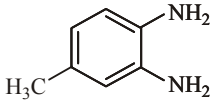
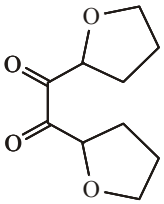
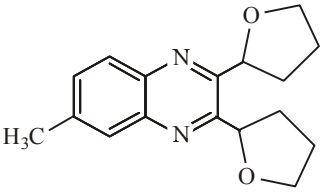
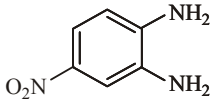
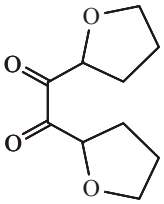
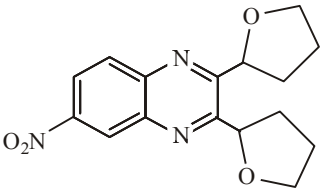
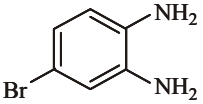
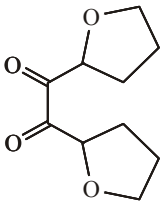
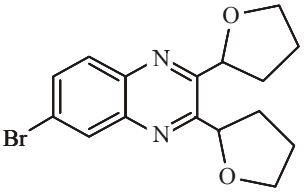
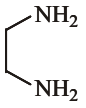
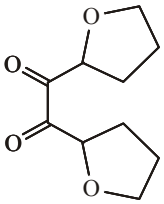
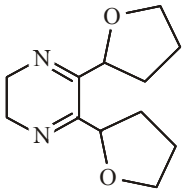
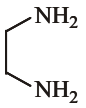
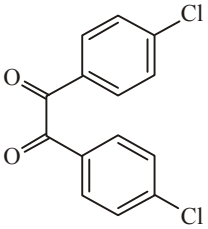
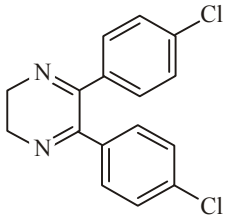
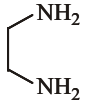
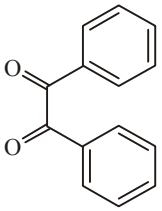
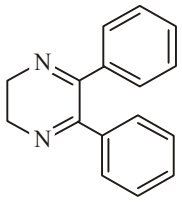
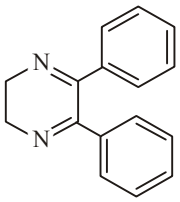
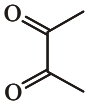
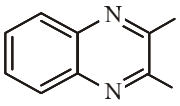
Entry	1, 2-Diamine (a)	1,2 Diketone	Product (b)	Time (min)	Yield (%)
9.				10	95
10.				10	97
11.				10	90
12.				10	91
13.				60	87
14.				60	85

Cont…

Entry	1, 2-Diamine (a)	1,2 Diketone	Product (b)	Time (min)	Yield (%)
15.				60	88
16.				60	30

[a] The substrate was treated with 1,2-diketones (2 mmol) by using 0.1 mmol of ZnO in the presence of hydrogen peroxide (1 mL) under neat conditions at room temperature.
[b] All products were identified by their IR and ^{1}H NMR spectra
[c] Isolated yields.

Table 3, Product (2b)

IR (KBr): 1349, 1523, 1616, 2981, 3475 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$): δ = 6.8 (m, 2H, J=7.01Hz), 7.2 (d, 2H, J=7.01Hz) ; 8.1 (d, 2H, J=7.01Hz); 8.4((d, 2H, J=8.12Hz); 8.7 (s, br, 1H, NH)

Table 4, Product (1b)

IR (KBr): 697,770, 1211, 1346, 1578, 1675, 1659, 3058 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$): δ = 7.55 (m, 5H), 7.35 (m,5H) ; 8.0 (d, 2H, J=8 Hz); 8.2(m,2H, J=8 Hz)

CONCLUSIONS

In conclusion, a method has been described in which ZnO/H_2O_2 is working as a highly efficient catalyst for the synthesis of benzimidazole and quinoxaline derivatives. The advantages include low cost, ease of catalyst handling, mild reaction conditions and reactions carried out at room temperature with excellent yields.

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