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Synthesis of 2-Substitued Benzimidazoles Using P_2O_5-SiO_2

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ABSTRACT

P_2O_5-SiO_2 (30% w/w) was found to be a useful catalyst for the synthesis of various 2-substituted aryl benzimidazoles under solvent-less and in solvent conditions from *o*-phenylenediamine and aldehydes. The products were directly recrystallized from methanol.

***Keywords**: P_2O_5/SiO_2, Solvent-free, Benzimidazole, o-Phenylenediamine, Supported catalyst*

1. Introduction

The benzimidazole moiety is found in various bioactive compounds having antiviral, antiulcer, antihypertension and anticancer properties [1-6]. The traditional methods for the synthesis of benzimidazoles involve treatment of *o*-phenylenediamines (OPD) with carboxylic acids or various derivatives under strongly acidic conditions or with aldehydes followed by oxidation [7-18]. Although these methods are suitable for certain synthetic conditions, sometimes, there exist some drawbacks such as long reaction time [19], high temperature [20], use of microwave oven [21], corrosive reagents and large amounts of solid supports which would eventually result in the generation of a large amount of toxic waste [22].

Phosphorus pentoxide-silica gel is an inexpensive, heterogeneous catalytic system which has been used in several transformations, such as oxidation of sulfides to sulfoxides [23], Schmidt reaction [24], and conversion of aldehydes to acylals [25]. As well as, we have reported catalytic applicability of P_2O_5-SiO_2 as an efficient and recyclable Catalyst for *N*-Acylation of Sulfonamides [26].

In continuation of our interest toward the development of new and cleaner methods for classical synthesis [27-32], we report herein the results of the preparation of 2-substituted benzimidazoles catalyzed by P_2O_5-SiO_2 under solvent and solvent-free conditions at room temperature (Scheme 1).

2. Experimental

All chemicals were purchased from Merck or Fluka chemical companies. ^{1}H NMR spectra were recorded with a Bruker-Avance AQS 300 MHz. The melting points were determined using an electrothermal digital melting point apparatus and are uncorrected. Reaction courses and product mixtures were monitored by thin layer chromatography.

2.1. Preparation of the P_2O_5/SiO_2 Reagent

A mixture of phosphorus pentoxide (5 g) and chromatography-grade silica gel (5 g) were placed in a flask and stirred for 4 h. This homogeneous, free-flowing, white powder reagent is sensitive toward moisture and should be stored in a desiccator.

2.2. General procedure for synthesis of 2-substituted benzimidazoles catalyzed by P_2O_5-SiO_2 under solvent-free conditions

OPD (1 mmol), aldehyde (1 mmol) and P_2O_5-SiO_2 (30% w/w, 0.4g) were ground together in a mortar with a pestle at room temperature for 20 min. Progress of the reaction was monitored by TLC. After completion of the reaction, hot methanol (10 ml) was added and the solid materials were removed by filtration. The filtrate product was allowed to stand at room temperature, the target molecules were produced and then collected by filtration. The products were identified by comparison of their physical data with those prepared in accordance with the literature procedures.

2.3. General procedure for synthesis of 2-substituted benzimidazoles catalyzed by P_2O_5-SiO_2 in CH_3CN

P_2O_5-SiO_2 (30% w/w, 0.4g) was added to a mixture of OPD (1 mmol) and aldehyde (1 mmol) in acetonitrile (5 mL). The mixture was stirred at room temperature, and the progress of the reaction was monitored by thin-layer

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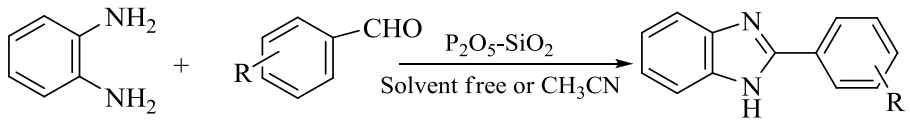


Scheme 1.

Table 1. Effect of various Lewis acids on the reaction of *o*-phenylenediamine with 4-nitrobenzaldehyde.

Entry	Catalyst	Time (min)	Yield (%)[a]
1	SiO_2	300	0
2	P_2O_5/SiO_2	30	85
3	$Cu(OAc)_2.2H_2O$	120	47
4	$Co(OAc)_2.4H_2O$	60	73
5	$Zn(OAc)_2$	90	70
6	$Zn(NO_3)_2.2H_2O$	180	65
7	$Zn(HSO_4)_2$	50	85

[a]Isolated yields.

chromatography (TLC). After completion of the reaction, the solvent was evaporated, and the crude product was dissolved in 5mL of methanol. The mixture was heated, and solid materials were removed by filtration. The filtrate product was allowed to stand at room temperature; the target molecules were produced and then collected by filtration.

2.4 Selected physical and spectral data

2-(4-Methoxyphenyl)-1H-benzimidazole (6), mp: 226–228 ºC. ^{1}H NMR (DMSO-d_6 ppm) δ: 3.82 (s, 3H, OCH_3), 7.25–7.73 (m, 8H, aromatic), 12.99 (bs, NH).

2-(3-Nitrophenyl)-1H-benzimidazole (8), mp: 201–203 ºC. ^{1}H NMR (aceton-d_6 ppm) δ: 7.31–8.62 (m, 8H, aromatic), 12.20 (bs, NH).

2-(4-Chlorophenyl)-1H-benzimidazole (9), mp: 290-292ºC. 1H NMR (DMSO-*d6* ppm) δ: 7.18- 8.08 (m, 8H, aromatic), 12.70 (bs, NH).

3. Results and discussion

3.1. Influence of various lewis acid on synthesis of benzimidazoles

We first investigated the catalytic activity of various Lewis acids, which promoted the model reaction of *o*-phenylenediamine (1 mmol) with 4-nitrobenzaldehyde (1 mmol) in CH_3CN at room temperature (Table 1). This result suggests that a Lewis acid catalyst plays a critical role in this reaction. P_2O_5-SiO_2 was highly effective catalysts for the present reaction. The catalytic activities of $Zn(HSO_4)_2$ was also similar to that of P_2O_5-SiO_2. $Zn(OAc)_2$, $Co(OAc)_2.4H_2O$ and $Zn(NO_3)_2.2H_2O$ were good catalysts for this reaction but catalytic activity for this reaction was lower than P_2O_5-SiO_2. $Cu(OAc)_2.2H_2O$ was less active as a catalyst.

3.2. Influence of P_2O_5-SiO_2 with different P_2O_5 loading

As expected SiO_2 showed no product formation. In the absence of P_2O_5, the reaction did not yield any product at room temperature even after a long reaction time (24 h). Next, P_2O_5-SiO_2 with different P_2O_5 loadings were used and it was observed that as P_2O_5 loading increased from 10-30 Wt% the yield of 2-(4-nitrophenyl)-1H-benzimidazole also increased. However, on further increasing the P_2O_5 loading to 50, 70 and 100 wt% the yield decreased with the formation of side products. Thus 30 wt% of P_2O_5-SiO_2 was used as the preferred catalyst for further studies (Table 2).

3.3. Influence of catalyst concentration

The effect of catalyst concentration on the given reaction protocol was studied. It was found that as the concentration of P_2O_5-SiO_2 30% was increased from 0.01g to 1 g (Table 2; entries 8–12) yield of the desired benzimidazole also increased. Hence 0.4 g of P_2O_5-SiO_2 catalyst was chosen as the optimum concentration.

3.4. Influence of solvent for synthesis of benzimidazoles

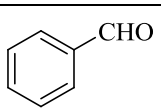
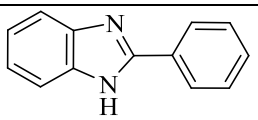
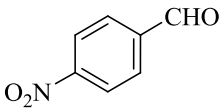
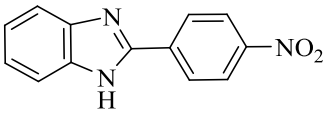
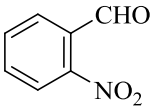
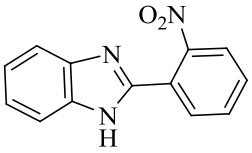
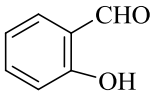
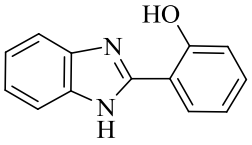
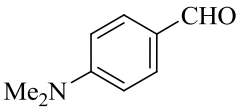
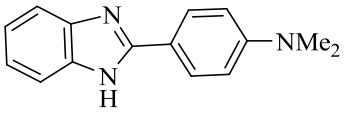
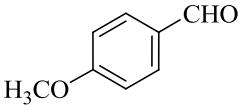
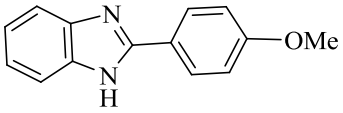
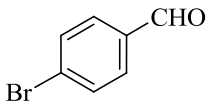
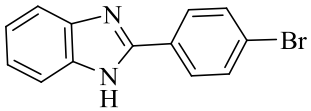
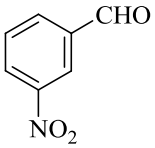
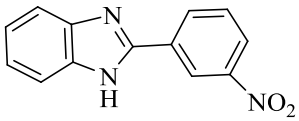
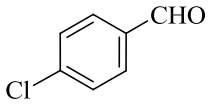
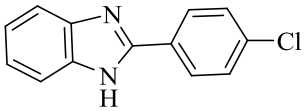
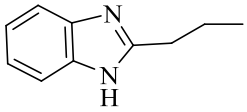
To choose the most appropriate medium in this heterocyclization reaction, the condensation of OPD and 4-nitrobenzaldehyde was examined at room temperature in the presence of a catalytic amount of P_2O_5/SiO_2 in various solvents. It seems that $CHCl_3$, CCl_4, CH_3CN, and C_2H_5OH gave excellent conversions. CH_3CN was the best among the solvents tested, but, we find that the reaction proceeded best under solvent-less conditions rather than using solvents.

Table 2. Effect of P_2O_5-SiO_2 on the synthesis of 2-(4-nitrophenyl)-1H-benzimidazole.[a]

Entry	Catalyst amount	Time (min)	Yield (%)[b]
Effect of P_2O_5 loading (wt%)			
1	0	24h	0
2	10	65	32
3	20	50	52
4	30	30	70
5	50	20	66
6	70	15	50
7	100	5	30
Effect of P_2O_5-SiO_2 loading (g)			
8	0.01	190	70
9	0.2	75	76
10	0.4	30	85
11	0.6	20	85
12	1	5	82

[a]Reaction conditions: benzaldehyde (1 mmol), OPD (1mmol), CH_3CN (5 ml) at room temperature.
[b]Isolated Yields.

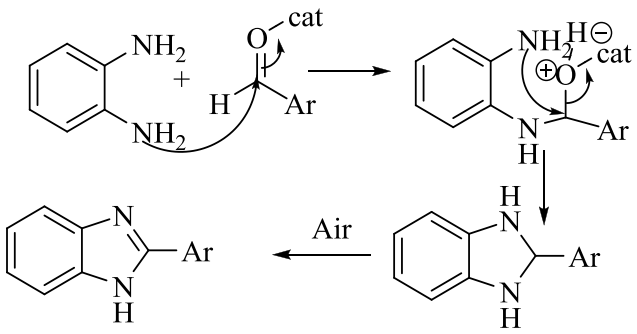
Table 3. Synthesis of benzimidazole derivatives from aldehydes and *o*-phenylenediamine[a].

Entry	Aldehyde	Product	Yield (%)		References
			CH_3CN	Solvent-free	
1			85	87	33
2			80	92	17
3			70	90	17
4			70	90	17
5			83	92	17
6			70	80	35
7			85	90	35
8			85	85	33
9			88	89	33
10			25	33	34

[a]Reactions were performed at room temperature by using 1 mmol of aldehydel, 1 mmol diamine, P_2O_5-SiO_2 (0.4g).
[b]The products were characterized by comparison of melting points and ^{1}H NMR with those prepared in accordance with the literature procedures.

3.5. Synthesis of 2-substituted benzimidazoles in the presence of P_2O_5-SiO_2 in solvent and under solvent-free conditions

To demonstrate the generality and scope of this method, we examined the reaction of o-phenylenediamine with a number of differently substituted aryl aldehydes both in CH_3CN and under solvent-free conditions. The results of this study are presented in Table 3.The results show that the efficiency and the yield of the reaction in solutions were much less than these observed under solvent-free conditions (Table 3).



Scheme 2.

According to the results, solvent-free condition is suitable for synthesis of 2-arylbenzimidazoles.

As table 3 shows, aromatic aldehydes, having different substituents such as methoxy, chloro, bromo, etc. were converted to the corresponding benzimidazoles in good to excellent yields (Table 3). The rates and yields of the reactions were influenced by the nature of the substituents present on the substrates and on steric factors. Reactions with substrates having electron-withdrawing groups such as nitro, proceeded at faster rates than those with electron-donating groups such as *N,N-p*-dimethylamino, while *ortho*-substituted aldehydes gave products in lower yields than *m*- and *p*-substituted examples. Aliphatic aldehydes also reacted with OPD under similar conditions to give the corresponding 2-alkylbenzimidazoles. However, the yields were lower than that of the aromatic aldehydes (Table 3; entry 10). The proposed mechanism for synthesis of 2-substituted benzimidazoles may be visualized to occur via reactions as depicted in Scheme 2.

In order to assess the capability of the present method with respect to the reported methods for the preparation of 2-substituted benzimidazoles from OPD and aromatic aldehydes, the synthesis of 2-(4-nitrophenyl)-1H-benzimidazole was compared with the reported methods (Table 4). As it is clear from Table 4, the present method is more efficient.

Finally, recycling experiments were conducted to find out the stability of the catalyst after the reaction. After completion of the reaction, the mixture was filtered to separate the catalyst. The efficiency of the recovered catalyst was verified with entry 2. Using the fresh catalyst, the yield of desired product was 92%, while the recovered catalyst in the three subsequent runs gave the yield of 88%, 82%, and 75%, respectively and color of the catalyst change to pink.

4. Conclusions

In conclusion, P_2O_5-SiO_2 is an inexpensive, easily available, noncorrosive environmentally benign compound. In this work, we have reported a convenient and efficient procedure for the preparation of benzimidazoles in good yields and short reaction times. The notable advantages of this methodology are direct use of a wide variety of aldehydes, operational simplicity, generality, availability of reactants and easy work-up.

Table 4. Comparative the synthesis of 2-(4-nitrophenyl)-1H-benzimidazole using the reported methods versus the present method

Entry	Reagent	Conditions	Time (h)	Yield (%)	Ref.
1	aluminosilicate	CH_3CN, reflux	4	92	10
2	[Hbim]BF_4	IL, r.t	2	90	8
3	$(CH_3)_2SBr$	CH_3CN, r.t	4	86	9
4	Yb$(OTf)_3$	$C_{10}F_{18}$, 90°C	6	93	13
5	P_2O_5-SiO_2	Solvent-free, r.t	20 min	92	-

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