A FAST PROCEDURE FOR THE PREPARATION OF BENZIMIDAZOLE DERIVATIVES USING POLYMER-SUPPORTED WITH TRIFLUOROMETHANESULFONIC ACID AS NOVEL AND REUSABLE CATALYST

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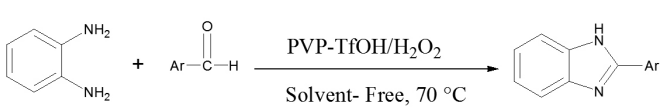
ABSTRACT

A highly selective synthesis of benzimidazoles from the reaction of o-phenylenediamines and aromatic aldehydes in the presence of PVP- trifluoromethanesulfonic acid is reported, and morphological investigation was reported by FT-IR. The remarkable advantages of this method are the simple experimental procedures, shorter reaction times, high yields of product, and non-toxic catalyst. However, the reactions were performed in solvent-free and the catalyst could be reused for several runs.

Keywords: Green chemistry; polymer-supported reagents; Benzimidazoles; reusable catalyst

INTRODUCTION

In the last ten years, supported reagents on polymers have become increasingly applied in organic synthesis [1], because the reactions are carried out with simple work-up, easy product isolation, and mild reaction conditions [2]. Benzimidazole is a kind of substances which have found practical applications in organic synthesis [3], and the benzimidazole nucleus are found in a variety of pharmaceuticals as cardiotonic agents,[4] potential antitumor [4] poli(ADP-ribose) phosphorilase inhibitors, [5] Histamine H4 receptor binders, [6] antiparasitic, [7] cardiovascular, [8] anticancers, [4] antimicrobials, [9] and antihypertensives, [9]. Due to the high importance of 2-aryl-1H-benzimidazoles for the preparation of biologically active molecules, their synthesis has been received considerable attention. The condensation of 1,2-phenylendiamines with carboxylic acids or their derivatives in the presence of strong acids such as mineral acids [10] or polyphosphoric acid [11] and the thermal or acid-promoted cyclization of N-(N-arylbenzimidoyl)-1,4-benzoquinoneimines [12] was include the methods of benzimidazole synthesis [13]. Direct condensation of o-aryldiamines and aldehydes is not a good synthetic reaction, as it is well known to yield a complex mixture. In this case, the addition of transition metal, namely copper (II) acetate [14], catalyzed by $Fe(ClO_4)_3$ [15], mercury oxide [16] or lead tetracetate [17] allow a partial selective synthesis of benzimidazoles. In recent years, solvent-free synthesis of benzimidazoles under microwave irradiation using $Yb(OTf)_3$ [18], Lithium bromide catalyzed [19], KSF clay[20], PPA[21], metal halide supported alumina[22] and solid support[23] have been reported. Unfortunately, many of these processes suffer some limitations, such as drastic reaction conditions, low yields, boring work up procedures and co-occurrence of several side reactions. Therefore, the development of a cost effective, safe and environment friendly reagent system is desirable. In addition to, organic synthesis in the absence of a solvent is a powerful tool for the generation of structurally diverse molecules. Solvent-free reactions often, have special selectivity, are easy to set-up and work-up, and are faster, which have aroused great interest [24]. These aspects, coupled with the lower overall costs of running a reaction without solvent and no specially needed equipment, could become a decisive factor in industry. Herein, we wish to disclose a novel protocol for the rapid synthesis of a variety of benzimidazoles using a catalytic amount of PVP-TfOH under solvent-free conditions, and the reaction of this supported reagent is simple work-up, easy product isolation, and mild reaction conditions. However, the reaction was carried out in neat at 70 °C for 6 minutes, using o-phenylenediamine (1 mmol), aldehyde (1.1 mmol), and H_2O_2 (30%, 3 mmol, 0.3 mL) in the presence of PVP- trifluoromethanesulfonic acid (0.2mg) (Scheme 1).



Scheme 1. Synthesis of Benzimidazole Derivatives in the presence of PVP–TfOH.

EXPERIMENTAL

Materials and Techniques

All reagents and solvents were purchased from Sigma-Aldrich and Merck, chemical companies. Yields refer to isolated pure products. The benzimidazoles derivatives were characterized by comparison of their spectral (IR, ^{1}HNMR), TLC and physical data with authentic samples, and the IR spectra of the samples (as KBr pellets) were recorded using a Rayleigh WQF-510 spectrophotometer in the range of 400– 4000 cm $^{-1}$. Melting points were determined using Electrothermal 9300 Melting Point. ^{1}H NMR and ^{13}CNMR spectra were recorded on Bruker 200 MHz and 50 MHz spectrometer.

Preparation of PVP-Tf_2O

A Trifluoromethanesulfonic acid (TfOH) (2.0 ml) was added to poly (4-vinylpyridine)(2 g), and it was stirred magnetically for 2h at room temperature. The suspension was filtered and washed with CH_2Cl_2 (2 × 5 ml) and the poly (4-vinylpyridine)-supported with tifluoromethansulfonic acid (PVP -TfOH) was obtained. The activity of this polymer was determined by potentiometric titration with a 0.1 N solution of NaOH. The activity of polymer was calculated (0. 1 g of catalysis equal to 0.08 mmol).

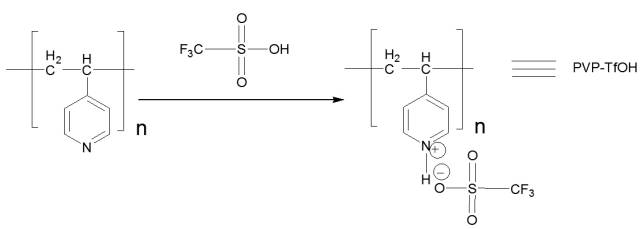
Typical Procedure for the Preparation of Benzimidazoles

A mixture of o-phenylenediamine (1 mmol), 4-chlorobenzaldehyde (1.1 mmol), and H_2O_2 (30%, 3 mmol), and PVP- TfOH (0. 2 g) was stirred magnetically for 6 min at 70 °C, and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture filtered and washed with CH_2Cl_2 (15 ml) there time. If further purification was needed, by recrystallization it was dissolved in EtOH (10 mL) and then poured into ice water (30 mL). The pure solid product was filtered, washed with ice water, and subsequently dried.

2-(4-Chlorophenyl)-1H-benzimidazole (Table 3, entry 1): mp 290-293°C; ^{1}H-NMR (200 MHz, DMSO-d6,): δ =7.10 (m, 2H), 7.30 (m, 2H), 7.6 (d, 2H, J=8.4 Hz), 8.20 (d, 2H), 12.5 (s, 1H, NH): 13 C-NMR (50 MHz, DMSO-d6): δ= 115.4, 123.2, 128.6, 128.9, 129.4, 134.3, 138.9, 152.9.

RESULTS AND DISCUSSION

In this study, we became interested to explore a new reagent (PVP-TfOH) for the synthesis of various benzimidazole derivatives, and the PVP-TfOH catalysis was prepared via a reaction of rifluoromethanesulfonic acid with poly (4-vinylpyridine) (Scheme 2).



Scheme 2

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The FT-IR spectrum of PVP and the PVP-TfOH catalyst was shown in (Fig 1). The catalyst is solid and solid state IR spectrum was recorded using the KBr disk technique. The Fig 1a is showed the FT-IR spectrum of PVP, and also the FT-IR spectrums (Fig 1b) is showed the new signals appeared to the signals observed for PVP. These new peaks are assigned to the C-F stretching from 1000 to 1400 cm^{-1} and sulfonates S=O stretching near 1175-1300cm^{-1} , S-O stretching near 1000-750 cm^{-1}, and broad OH stretching absorption around 3500 and 2800 cm^{-1}

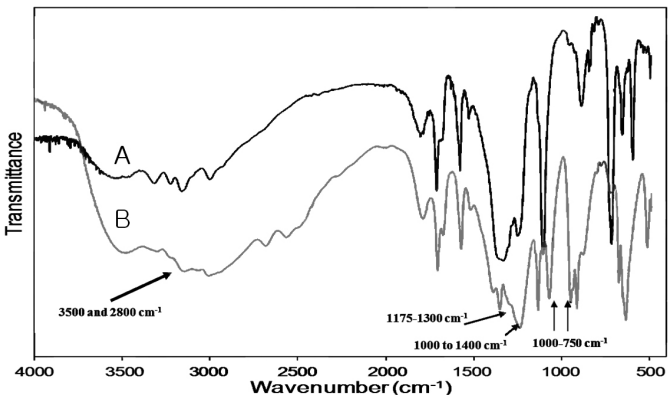
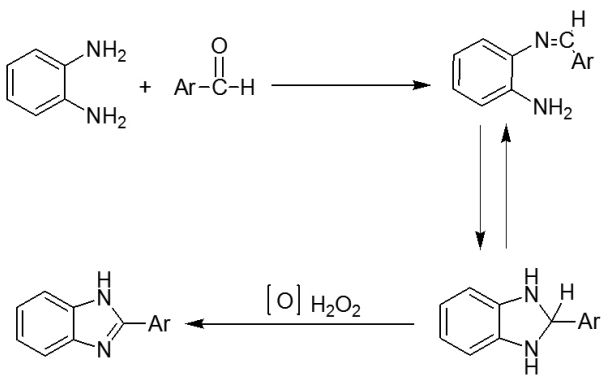


Fig 1. A) FTIR spectrum of poly (4-vinylpyridine) in KBr, and (B) PVP+TfOH

Initially, a reaction was carried out in neat at 70 °C, using o-phenylenediamine (1 mmol), 4-chlorobenzaldehyde (1.1 mmol), and H_2O_2 (30%, 3 mmol) in the presence of PVP-TfOH. With this optimistic result in hand, we further probed the best reaction condition by using different amounts of PVP- TfOH. An increase amount of catalyst from 0.1g to 0.2g not only decreased the reaction time from 9 min to 6 min but also increased the product yield from 90 to 95%. This showed that the catalyst concentration plays a major role in optimization of the product yield. Although the use of 0.3g of this catalyst permitted the reaction time to be decreased to 5 min, the yield is become persistent. These results indicate that the amount of catalyst is required (Fig.2a).

In the (Scheme 3) the suggested mechanism for the preparation of benzimidazoles was shown that the actual oxidant is H_2O_2. wherein the absence of H_2O_2 resulted in an extremely slow reaction in sufficient for complete product formation even after 15 h. whoever, imine derivative was obtained as only product. Also, different amounts of H_2O_2 in conditions as (Tables 3), and the results are depicted in (Fig.2b).



Scheme 3. The proposed mechanism for the preparation of benzimidazoles

To evaluate the effect of reaction temperature, the effect of temperature on the rate of reaction was studied at different temperatures for the preparation of benzimidazoles in the presence of PVP-TfOH system (Table 1). It was observed that the reaction was found to be very slow at room temperature. At 50 °C, the reaction proceeded smoothly and almost the complete conversion of the product was observed. Further increase in temperature to 70, 90 and 110 °C increased the rate of reaction. Therefore, we kept the reaction temperature at 70 °C (giving short reaction time and high yield).

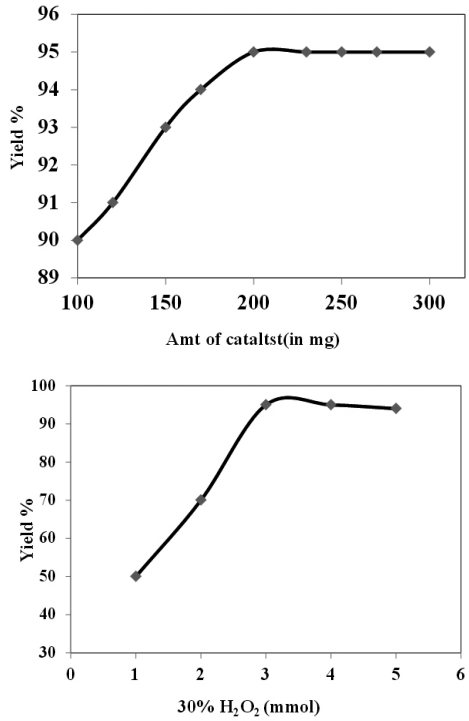


Fig.2. a) Effect of catalyst weight and b) Effect of Amounts of H_2O_2 (conditions as Tables 3).

Table 1. Effect of temperature for the preparation of 2-(4-chlorophenyl)-1H-benzo[d]imidazole under solvent-free using PVP-TfOH catalysts as catalyst (0.2 g).

Entry	Temperature(°C)	Time(min)	Yield (%)
1	rt	2h	60
2	50	15	95
3	70	6	95
4	100	4	95
5	110	4	96

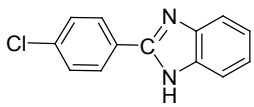
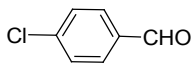
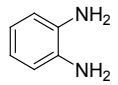
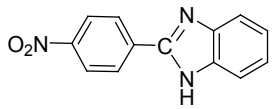
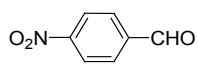
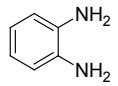
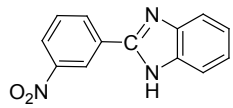
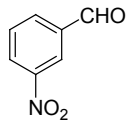
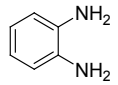
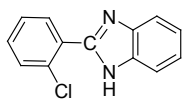
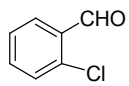
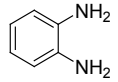
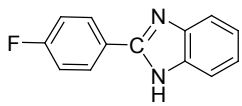
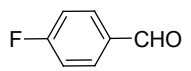
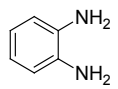
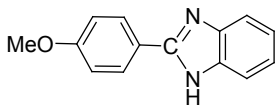
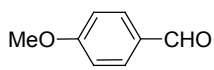
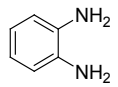
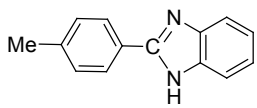
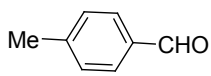
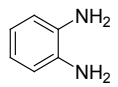
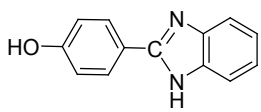
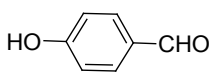
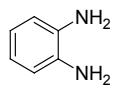
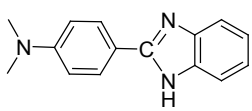
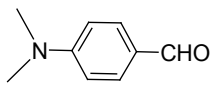
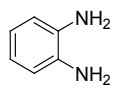
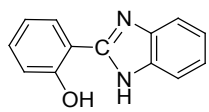
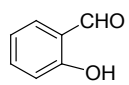
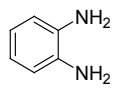
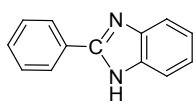
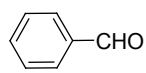
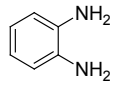
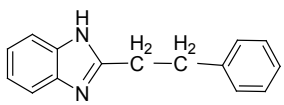
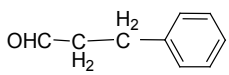
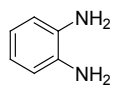
Certainly, solvent plays a critical role in the reactions; therefore, we decided to investigate the effect of various solvents and select an appropriate condition for the preparation of benzimidazole. Therefore, we screened different solvents such as acetonitrile, ethanol, THF, acetonitrile, water, toluene, and solvent free for the preparation of benzimidazole, as a typical example, the 4-chlorobenzaldehyde and 1,2-phenylendiamine as substrates in the presence of (0. 2 g) catalyst and H_2O_2 (3 mmol)in different solvents at 70°C (Table 2). Solvent -free was found to be the most efficient for this transformation. The reactions in other solvents required longer reaction time and low yield

Table 2. Reaction of chlorobenzaldehyde, 1,2-phenylendiamine under 6 min conditions.

Entry	Solvent [a]	Yield (%)
1	Ethyl acetate	62
2	Acetonitrile	20
3	Ethanol	62
4	n-hexane	10
5	H_2O	25
6	Solvent- Free	95
7	THF	30

[a] Refluxed

Table 3. Reaction conditions: o-phenylenediamine (1 mmol); aldehyde (1.1 mmol); H_2O_2 (30%, 3 mmol) in the presence of PVP-TfOH (0. 2g).

Time (min)/Yield (%)	Product	Substrates	Substrate	Entry
6(95)				1
5(96)				2
5(95)				3
6(94)				4
5(96)				5
15(90)				6
12(95)				7
8(96)				8
20(80)				9
12(93)				10
11(95)				11
15(90)				12

[a] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.
[b] Yields refer to pure isolated products.

The generality of this reaction was examined using several types of aldehydes with o-phenylenediamine under the optimized reaction conditions. In all cases, the reactions gave the corresponding products. In order to study the generality of this procedure, a series of benzimidazoles compounds were synthesized using several types of aldehydes. A ratio of 1,2-phenylendiamine(1mol), aryl aldehyde (1.1mol), H_2O_2 (3mmol), PVP-TfOH (0.2g) was found to be optimum for the cou-

pling of aryl aldehydes and 1,2-phenylendiamines and the results are presented in (Table 3). As shown, variety of substituted aromatic aldehydes such as either electron-donating (Table 3, entry 7-11) or electron-withdrawing, substituents (Table 3, entry 2-6) were successfully employed to prepare the corresponding benzimidazole derivatives in excellent yields. In addition, aryl and alkyl aldehydes could also be used for efficient preparation of various heterocyclic-benzimidazoles (Table 3, entry 11 and 12).

The re-use of PVP/ TfOH was investigated in the reaction between 4-chlorobenzaldehyde, o-phenylenediamine (1 mmol), 4-chlorobenzaldehyde (1.1 mmol), and H_2O_2 (30%, 3 mmol, 0.3 mL). After completion of the reaction, the reaction mixture was filtered, and the catalyst was recovered after each run, washed three times with acetone, dried in a room temperature prior to use and tested for its activity in the subsequent run and no fresh catalyst was added. The catalyst was tested three times. It was seen that the catalyst displayed very good reusability (Fig. 3).

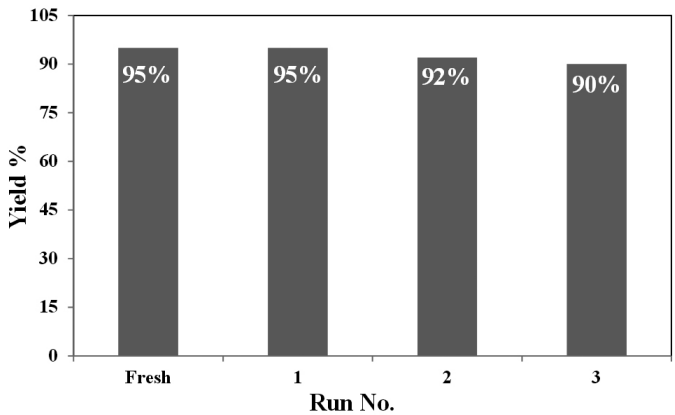


Fig. 3, Reusability of the catalyst (conditions as in Tables 3)

CONCLUSIONS

In summary, we have developed a new polymer-supported by Trifluoromethanesulfonic for the synthesis of benzimidazoles. Our method has several advantages including short reaction times, mild conditions, excellent yields, inexpensive and non-toxic catalyst, simple operation and work-up. Additionally, the protocol does not require volatile and hazardous organic solvents and an additional ultrasound or microwave oven. The elimination of the solvent has obvious environmental benefits with regard to the depletion of solvent waste. Also the catalyst could be successfully recovered at least for three runs without significant loss in activity.

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SUPPLEMENTARY MATERIAL:

Complete experimental procedures and relevant spectra (^{1}H NMR and ^{13}C NMR spectra) for some compounds. This material is available in Supporting Information

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