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Facile Route for the Synthesis of Benzothiazoles and Benzimidazoles in the Presence of Tungstophosphoric Acid Impregnated Zirconium Phosphate under Solvent-Free Conditions

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ABSTRACT: *Rapid and efficient condensation reactions of o-phenylenediamine and o-aminothiophenol with various aldehydes were carried out using tungstophosphoric acid impregnated zirconium phosphate in solvent-free conditions to afford the corresponding 2-substituted arylbenzimidazole and arylbenzothiazole derivatives in good to excellent yields. This procedure constitutes a simple and practical green synthetic method for 2-arylbenzimidazoles and 2-arylbenzothiazoles and their structural analogs. Furthermore, the catalyst can be reused for several times but it will be less active.* Heteroatom Chem 20:202–207, 2009; DOI 10.1002/hc.20534

INTRODUCTION

Benzimidazoles and benzothiazoles are very important groups of heterocyclic compounds that have many applications in both pharmaceutical and industrial research. They are widely used in bio-organic and medicinal chemistry with wide applications in drug discovery such as antiviral, anticonvulsant, antiulcer, anti-inflammatory, antiparasitic, antihelmintic, antiallergic, anticoagulant, and antitumor applications [1]. For example, 2-(4-aminophenyl)benzothiazoles exhibit nanomolar inhibitory activity against a range of human breast, ovarian, colon, and renal cell lines in vitro [2]. They are also used in industry as antioxidants, vulcanization accelerators, as a dopant in a light-emitting organic electroluminescent device [3]. They are also applied in agriculture as strobilurin derivatives (agricultural fungicides) [4]. Several methods have been developed for the preparation of these heterocycles including the condensation of carboxylic acids [5], acid chlorides [6], nitriles [7], orthoesters [8], amides [9], esters [10], or aldehydes [11] with *o*-aminothiophenols, and *o*-phenylenediamine (OPD). In another method, 2-mercapto and 2-chlorobenzothiazoles have been prepared by classical cyclization of the corresponding ortho-haloanlines with potassium/sodium *O*-ethyl dithiocarbonate [12].

However, most of these methods have following drawbacks: high thermal conditions, long reaction

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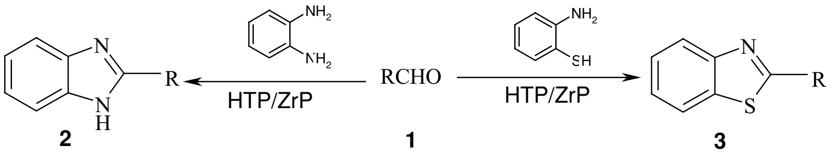

SCHEME 1 Synthesis of benzimidazoles (**2**) and benzothiazoles (**3**).

times, low yields of the products, harsh reaction conditions, and the use of toxic metallic compounds that result in waste streams.

In recent decades, the use of heteropolyacids (HPAs) as catalysts for fine organic synthetic processes has been developed and is important for industries related to fine chemicals [13], including flavors, pharmaceuticals, and food industries [14,15]. Solid heteropolyacids have attracted much attention in organic synthesis owing to easy workup procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of the catalysts [16]. For heterogeneous systems, it is possible to control solid strength by supporting HPAs on different carriers [17]. An immobilization of HPAs on a number of porous supports such as silica, active carbon, montmorillonite K-10, zeolite, zirconium phosphate and so on [17–22] was, therefore, extensively studied.

In continuation of our previously reported catalytic properties of heteropolyacids [23], herein, we wish to report a suitable method for the use of zirconium phosphate (ZrP) as inorganic support with the Keggin-type polyoxometalate (POM), $H_3PW_{12}O_{40}$ (denoted as HTP hereafter) as heterogeneous catalyst for the synthesis of 2-arylbenzimidazole (**2**) and 2-arylbenzothiazole (**3**) derivatives (Scheme 1).

RESULTS AND DISCUSSION

Physicochemical Characterization

Figure 1 shows the FT-IR spectra of the 40 wt% samples of HTP-impregnated ZrP. From the FT-IR spectra, it was found that at 110°C-dried samples the Keggin bands are observed at 1064, 815, and 607 cm^{-1} for HTP/ZrP. The FT-IR spectra of HTP/ZrP indicate that most of characteristic bands of the parent Keggin structure, could be found in the HPA fingerprint region (1250–500 cm^{-1}), are not shown or appeared in the same assignable position of the bands correspond to ZrP host material. The observed band at 516 cm^{-1} may be attributed to the δ(P—O) vibration. Moreover, the band located at 1633 cm^{-1} may be characteristic of the O—H stretching vibration [18]. Figure 2b shows the XRD pattern of 40 wt% of HTP-impregnated ZrP dried at 110°C. It can be observed that the impregnated products are crystalline. Some peaks of HTP overlapped with that of zirconium phosphate. This may be due to the interaction of HPA with that of the support.

Synthesis of 2-Arylbenzothiazoles and 2-Arylbenzimidazoles in the Presence of Catalytic Amounts of Polyoxometalate under Solvent-Free Conditions

At first, for optimization of the reaction conditions, the reaction of 4-methoxybenzaldehyde (1 mmol) with OPD (1.5 mmol) in CH_3CN at room temperature in the presence of a catalytic amount of HTP (5 mol%) was studied. The analysis of the reaction mixture showed the desired product 2-(4-methoxyphenyl)-1*H*-benzimidazole was produced only in 55% yield after 15 min plus unreacted starting materials (Table 1, entry 2). Then, we decided to study the catalytic ability of the supported HTP on ZrP. We observed that the reaction of 4-methoxybenzaldehyde (1 mmol) with OPD (1.5 mmol) in CH_3CN in the presence of the supported catalyst (40% HTP/ZrP, 5 mol%) was performed smoothly and the desired product 2-(4-methoxyphenyl)-1*H*-benzimidazole was obtained in 78% yield after 15 min (Table 1, entry 4). We have also studied the above-mentioned reaction in the presence of pure ZrP (Table 1, entry 1). Although this catalyst (ZrP) was active for the condensation reactions, but the yields were insignificant when compared to those with the supported catalysts. These results show the strong synergistic effects of ZrP upon the catalytic activity of HTP in the reaction of 4-methoxybenzaldehyde with OPD (Table 1). In addition, because of the current challenge for developing solvent-free and environmentally benign protocols [15], we studied the reaction of 4-methoxybenzaldehyde (1 mmol) with OPD (1.5 mmol) under solvent-free conditions in the presence of HTP/ZrP (Table 1, entry 9). We found that the solvent-free condition was more suitable and efficient to complete the reaction within 15 min. The results of this study are presented in Table 1.

From the results presented in Table 1, the reaction conditions we chose were *o*-phenylenediamine

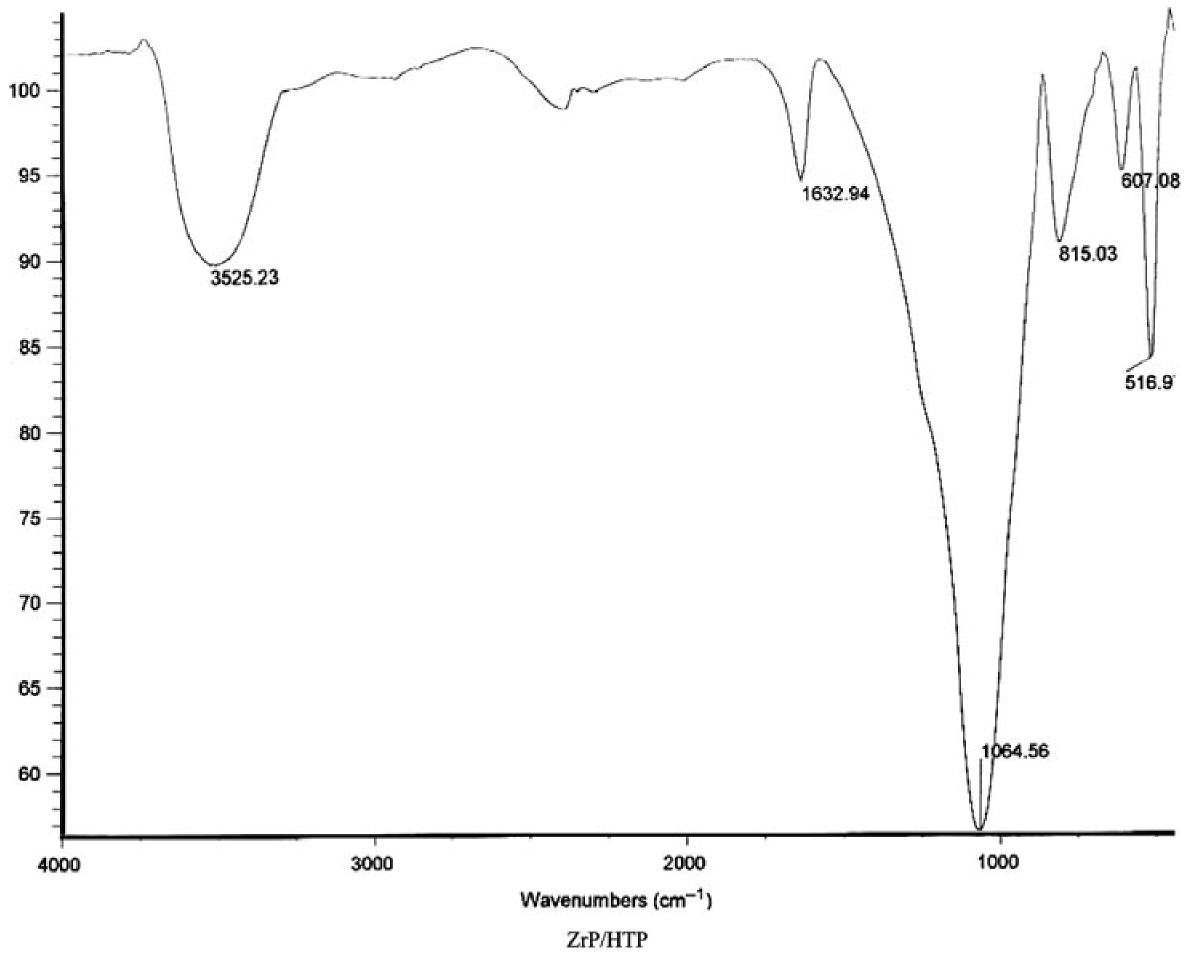

FIGURE 1 FTIR spectra of 40 wt% HTP/ZrP, dried at 110°C.

(1.5 mmol), aldehydes (1 mmol), and 50% HTP/ZrP (0.1 g, 3 mol%). Under these reaction conditions, we performed a series of experiments for reactions of OPD and *o*-aminothiophenol with different aldehydes under solvent-free conditions. The results are summarized in Table 2, and both aldehydes bearing electron-donating (Table 2, entries b–e) and electron-withdrawing (Table 2, entries f, g) substituents gave desired benzimidazoles in excellent yields. Heteroaryl aldehydes, such as 2-furyl and 2-pyridyl (Table 2, entries h, i), were well tolerated under these conditions. Aliphatic aldehydes also reacted with OPD and *o*-aminothiophenol under similar conditions to give the corresponding 2-arylbenzimidazoles and 2-alkylbenzothiazoles. However, the yields were lower than that of the aromatic aldehydes (Table 2, entry j).

Recovery

The feasibility of reusability of the catalyst was also examined with 4-methoxybenzaldehyde as a model substrate in the presence of HTP/ZrP under solvent-free conditions. In typical reactions, catalyst was simply filtered from the reaction mixture, washed with ethanol, dried and calcinated at 350°C for 4 h, and reused for five runs (Table 3). On the basis of observations made from different experiments, one

TABLE 1 Synthesis of 2-Arylbenzimidazoles[a] in different conditions after 15 min

Entry	*Catalyst*	*Solvent*	*Yield (%)*
1	ZrP (0.2 g)	CH_3CN	21
2	HTP (5 mol%)	CH_3CN	55
3	HTP/ZrP (3 mol%)[b]	CH_3CN	68
4	HTP/ZrP (5 mol%)	CH_3CN	78
5	HTP/ZrP (7 mol%)	CH_3CN	78
6	HTP/ZrP (5 mol%)	CH_2Cl_2	45
7	HTP/ZrP (5 mol%)	MeOH	60
8	HTP/ZrP (5 mol%)	EtOH	43
9	HTP/ZrP (5 mol%)	Solvent-free	95

[a] Reaction conditions: 1 mmol of 4-methoxybenzaldehyde with OPD (1.5 mmol) at room temperature was used.
[b] HTP/ZrP (40% w/w).

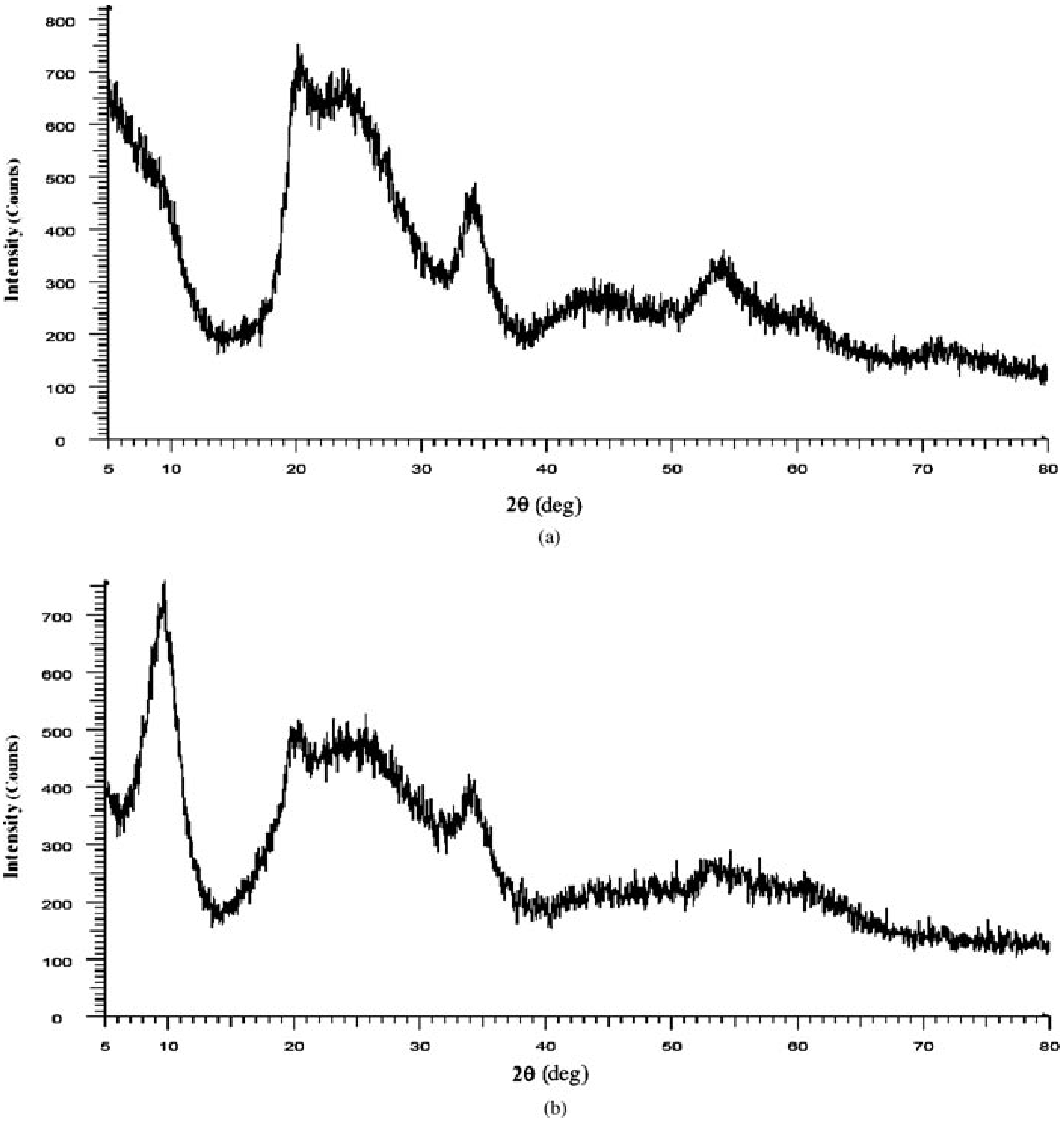

FIGURE 2 XRD patterns of (a) ZrP and (b) 40 wt% HTP/ZrP, dried at 110°C.

can conclude whether the recovered catalyst is calcinated after drying; the activity of the catalyst will increase. Supposedly, adsorbed water in the reaction will decrease the activity of the catalyst. The reaction proceeded smoothly with a yield of 95%–82%, and this result indicates that the catalyst can be reused but it will be less active.

EXPERIMENTAL

All solvents and reagents were purchased from Fluka or Merck. The X-ray powdered diffraction patterns were recorded on a Philips PW 1710 diffractometer with automatic control. The patterns were run with monochromatic Cu Kα radiation with a scan rate of 2° min^{-1}. The products were purified by column or thick layer chromatography techniques. FT-IR spectra were obtained as potassium bromide pellets in the range 400–4000 cm^{-1} with Nicolet Impact 400 D. ^{1}H NMR spectra were recorded with a Bruker-Avance AQS 300 MHz.

Preparation of Zirconium Phosphate

Zirconium phosphate was prepared by taking 1 M aqueous solution of $ZrOCl_2 \cdot 8H_2O$ and it was slowly added to ten time excess of 1 M H_3PO_4. The precipitate was washed several times with de-ionized water, dried 2 h at 368 K, and stored at 100% relative humidity and room temperature [24].

$$ZrPO_4\ (ZrP) + H_3PW_{12}O_{40}\ (HTP) \xrightarrow[H_2O,\ r.t.]{assembly} \xrightarrow[for\ 4\ h\ at\ 110°C]{were\ dried} \xrightarrow[for\ 4\ h\ at\ 350°C]{were\ calcined} HTP/ZrP$$

SCHEME 2 Representation of HTP/ZrP preparation.

TABLE 2 Synthesis of Benzothiazoles and Benzimidazoles[a] Catalyzed by HTP/ZrP after 15 min

Entry	*R*	*Yield (%)*[b] **2**[c]	**3**
a	Ph	85	92
b	2-MeO-C_6H_4	85	98
c	4-MeO-C_6H_4	95	95
d	2-OH-C_6H_4	98	92
e	4-OH-C_6H_4	90	85
f	3-NO_2-C_6H_4	92	95
g	4-NO_2-C_6H_4	80	87
h	2-Furyl	80	85
i	2-Pyridyl	80	80
j	C_5H_{11}	78	78

[a] *o*-Phenylenediamine (1.5 mmol), or *o*-aminothiophenol (1.5 mmol), aldehyde (1 mmol), and 40% HTP/ZrP (5 mol%).

[b] Isolated yield.

[c] Spectroscopic data for 2-(4-methoxyphenyl)-1*H*-benzimidazole (**2c**): Mp 165–167°C. ^1H NMR (DMSO-d_6): δ (ppm) = 3.82 (s, 3H, OCH_3), 7.25–7.73 (m, 8H, aromatic), 12.99 (bs, NH).

TABLE 3 Recycling of HTP/ZrP[a]

Run	*Yield (%)*
1	95
2	94
3	93
4	94
5	82

[a] *o*-Phenylenediamine (1.5 mmol), 4-methoxybenzaldehyde (1 mmol), and 40% HTP/ZrP (5 mol%).

Preparation of ZrP/HPA

The supported HTP catalyst was prepared by using the method of incipient wetness. In a typical process, a 640-mg portion of HTP was dissolved in deionized water and impregnated dropwise into 1600-mg ZrP support in 25 mL methanol with constant agitation. The resulting pastes were dried for 4 h at 110°C and calcined for 4 h at 350°C [22,23] (Scheme 2).

General Procedure for the Synthesis of 2-Arylbenzimidazoles and 2-Arylbenzothiazoles Catalyzed by $CU_{3/2}PMO_{12}O_{40}/SIO_2$ under Solvent-Free Conditions

OPD, or *o*-aminothiophenol (1.5 mmol), aldehyde (1 mmol), and 40% HTP/ZrP (5 mol%) were ground together in a mortar with a pestle at room temperature for 15 min. The progress of the reaction was monitored by TLC. At the end of the reaction, the reaction mixture was washed with cold diethyl ether and filtered to remove HTP/ZrP. Then, the organic solution was purified on a silica gel plate or a silica gel column (20% ethyl acetate in hexane). The products were identified by comparison of their physical data with those prepared in accordance with the literature procedures.

CONCLUSIONS

In summary, we developed a fast, simple procedure, and convenient method for the synthesis of benzimidazoles and benzothiazoles using HTP/ZrP, as an eco-friendly, inexpensive, and efficient catalyst without using a solvent. The salient features of this method include the simple reaction setups, mild reaction conditions, and short reaction time. These advantages render the synthesis of benzimidazoles and benzothiazoles and the related compounds more efficient and environmental friendly.

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