Facile one-pot synthesis of 2-arylbenzothiazoles catalyzed by H₃PO₄/TiO₂-ZrO₂ (1/1) under solvent-free conditions

Hossein Naeimi and Arash Heidarnezhad

ABSTRACT
A highly efficient and simple protocol for the preparation of 2-arylbenzothiazoles through condensation of 2-aminothiophenol and different aldehydes in the presence of H₃PO₄/TiO₂-ZrO₂(1/1)-cetyl pyridinium bromide (CPB) is described. The reaction proceeded under mild and solvent-free conditions to afford 2-arylbenzothiazole derivatives. In this method, the title compounds were obtained in good to excellent yields and short reaction times. The structures of synthesized products were identified by infrared, ¹H NMR, ¹³C NMR, and mass spectroscopy.

GRAPHICAL ABSTRACT

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Aldehyde; 2-aminothiophenol; 2-arylbenzothiazole; H₃PO₄/TiO₂-ZrO₂; synthesis

Introduction
Benzothiazole is a privileged bicyclic ring system. It contains a benzene ring fused to a thiazole ring. The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities such as antitumor,[¹,²] anti-Candidia,[³] anti-Parkinson’s,[⁴] anti-inflammatory, and antihistaminic activities. Benzothiazoles have also shown significant effect against cancer.[⁵] A variety of methods for the synthesis of 2-arylbenzothiazoles have been developed.[⁶,⁷] The most general approaches for synthesis of 2-arylbenzothiazoles include the following: (1) Oxidative cyclization of phenolic Schiff bases derived from the condensation of 2-aminothiophenols and aldehydes using various oxidants such as Sc(OTf)₃-molecular oxygen[⁸] and pyridinium chlorochromate[⁹] and (2) condensation of 2-aminothiophenols with carboxylic acids under microwave irradiation in the presence of a Lewis acid.[¹⁰,¹¹]

Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in industrial contexts. These reactions are effected by the reagents immobilized...
on the porous solid supports and have advantages over the conventional solution-phase reactions.\cite{12,13} The reactions on solid supports under solvent-free conditions are currently the subject of considerable attention from synthetic chemists who wish to develop ecofriendly techniques because these heterogeneous organic reactions have many advantages, such as ease of handling, low corrosion, minimum execution time, environmentally safe disposal, and waste minimization.\cite{14–21} Consequently, it is important to note that the combination of heterogeneous catalysis with the use of solvent-free conditions is a suitable way toward the so-called ideal synthesis.

During the past few years, different solid acid catalysts such as zeolites,\cite{22} metal cation-exchanged clays,\cite{23} ion exchange resins, supported-heteropolyacids,\cite{24} nano-sized Dodeca-tungstophosphoric acid (TPA)/\textit{ZrO}_2 dispersed in SBA-15 channels,\cite{25} TPA/\textit{ZrO}_2 dispersed in MCM-41 channels,\cite{26} and mixed metal oxides have been used for organic reactions. Phosphate-based solid acids have already been quite efficacious in several industrially important acid-demanding reactions.\cite{27,28} In addition, phosphate seems to enhance catalytic properties, to stabilize surface area and crystal phase, to improve the surface acidity, and to make the impregnated material porous.\cite{29}

With this research, we report an efficient one-pot synthesis of various substituted 2-arylbenzothiazoles from the reaction of 2-aminothiophenol and different aldehydes in the presence of catalytic amounts of H\textsubscript{3}PO\textsubscript{4}/\textit{TiO}_2–\textit{ZrO}_2 (1/1)–CPB under solvent-free and mild conditions.

**Results and discussion**

**Catalyst characterization**

To evaluate the crystalline structure of the optimized catalyst, the x-ray diffraction (XRD) pattern for the calcined sample at 500 °C after loading of 30 wt% H\textsubscript{3}PO\textsubscript{4} is shown in Fig. 1. In general, \textit{TiO}_2–\textit{ZrO}_2 (1/1)–CPB shows an amorphous form, but after the loading of H\textsubscript{3}PO\textsubscript{4}, the corresponding peaks of the crystalline TiO\textsubscript{2} phase and crystalline ZrO\textsubscript{2} phase are observed, which is in accordance with the previously reported work.\cite{30} Also, it can be seen that the crystalline structure of the \textit{TiO}_2–\textit{ZrO}_2 (1/1)–CPB remained intact after the immobilization of H\textsubscript{3}PO\textsubscript{4}, which is desirable for our catalytic purpose.

![XRD pattern of H\textsubscript{3}PO\textsubscript{4}/\textit{TiO}_2–\textit{ZrO}_2 (1/1)–CPB](image-url)

*Figure 1. XRD pattern of H\textsubscript{3}PO\textsubscript{4}/\textit{TiO}_2–\textit{ZrO}_2 (1/1)–CPB.*
In addition, scanning electron microscopy (SEM) image shows the external morphology of the calcined catalyst after loading of phosphoric acid (Fig. 2). By looking more closely at the image, the phosphoric acid layer on TiO$_2$–ZrO$_2$ (1/1)–CPB can be observed.

The energy dispersive x-ray (EDX) analysis indicates elemental analysis on areas as small as nanometers in diameter. As shown in Fig. 3, the presence of peaks related to Ti, Zr, P, and O confirmed the elemental identification and quantitative compositional information of H$_3$PO$_4$/ZrO$_2$–TiO$_2$ (1/1)–CPB catalyst.

The infrared (IR) spectra of the optimized H$_3$PO$_4$/ZrO$_2$–TiO$_2$ (1/1)–CPB catalyst is shown in Fig. 4. As reported earlier, the FT-IR spectrum of ZrO$_2$–TiO$_2$ (1/1)—CPB is not very informative, which is why it is not shown here. The characteristic peaks at approximately 750 and 1100 cm$^{-1}$ may be attributed to belong to the P–O–P and P–OH stretching, respectively.$^{[30]}$ The band at nearly 1600 cm$^{-1}$ also belongs to the O–H in-plane bending vibration. Moreover, the characteristic peak of O–H stretching vibration appeared in the 2100–3500 cm$^{-1}$ region.

Figure 2. SEM image of H$_3$PO$_4$–TiO$_2$–ZrO$_2$(1/1)–CPB.

Figure 3. EDX image of H$_3$PO$_4$–TiO$_2$–ZrO$_2$(1/1)–CPB.
Catalytic activity

After preparation and characterization of H$_3$PO$_4$/ZrO$_2$-TiO$_2$ (1/1)–CPB, the catalytic activity was investigated for the synthesis of 2-arylbenzothiazole under mild conditions. A reaction model between 4-nitrobenzaldehyde and 2-aminothiophenol as the substrates was investigated over the catalyst at room temperature (Scheme 1).

In order to optimize the reaction conditions and obtain the best catalytic activity, the reaction model was conducted in different reaction parameters such as solvent, amount of loading the H$_3$PO$_4$, and the amount of used catalyst. The corresponding results are summarized in Table 1. As can be seen, the best catalytic activity was observed using 40 mg catalyst and 30 wt% H$_3$PO$_4$ under solvent-free conditions.

Scheme 1. Synthesis of 2-(4-nitrophenyl)-benzothiazole.

Table 1. Effects of different reaction conditions on the synthesis of 2-(4-nitrophenyl) benzothiazole over H$_3$PO$_4$/ZrO$_2$-TiO$_2$ (1/1)–CPB.$^a$

| Entry | H$_3$PO$_4$ (wt%) | Catalyst (mg) | Solvent          | Yield (%)$^b$ |
|-------|-------------------|---------------|------------------|---------------|
| 1     | 10                | 30            | None             | 51            |
| 2     | 15                | 30            | None             | 63            |
| 3     | 20                | 30            | None             | 72            |
| 4     | 25                | 30            | None             | 82            |
| 5     | 30                | 30            | None             | 90            |
| 6     | 35                | 30            | None             | 78            |
| 7     | 30                | 40            | None             | 96            |
| 8     | 30                | 50            | None             | 96            |
| 9     | 30                | 40            | Dichloromethane  | 65            |
| 10    | 30                | 40            | Ethyl acetate    | 74            |
| 11    | 30                | 40            | Acetonitrile     | 68            |

$^a$The reaction occurred in the presence of 1 mmol of 4-nitro benzaldehyde, 1 mmol of 2-aminothiophenol, and various amounts of the catalyst.

$^b$Isolated yields.
Table 2. Synthesis of 2-arylbenzothiazoles using $\text{H}_3\text{PO}_4/\text{ZrO}_2-\text{TiO}_2$ (1/1)–CPB (40 mg, 30 wt% $\text{H}_3\text{PO}_4$) under solvent-free conditions at room temperature.

\[
\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{Product} & \text{Time (min)} & \text{Yield\textsuperscript{a} (%)} \\
1 & \text{Ph-CHC} & \text{NH} & 20 & 87 \\
2 & \text{Ph-CHO} & \text{OH} & 25 & 89 \\
3 & \text{MeO-Ph-CHO} & \text{MeO} & 25 & 86 \\
4 & \text{Ph-CHC} & \text{Me} & 30 & 64 \\
5 & \text{Me-Ph-CHC} & \text{Me} & 15 & 82 \\
6 & \text{Ph-CHC} & \text{Cl} & 20 & 87 \\
7 & \text{Cl-Ph-CHO} & \text{Cl} & 15 & 92 \\
8 & \text{Ph-CHO} & \text{NO}_2 & 30 & 80 \\
9 & \text{O}_2\text{N-Ph-CHO} & \text{O}_2\text{N} & 10 & 96 \\
10 & \text{Ph-CHC} & \text{Cl} & 20 & 75 \\
11 & \text{Ph-CHO} & \text{NO}_2 & 20 & 93 \\
12 & \text{H}_2\text{C(N(CH}_3)_2-Ph-CHO} & \text{N(CH}_3)_2 & 35 & 86 \\
\end{array}
\]

\textsuperscript{a}Isolated yields.
After optimizing the reaction conditions, synthesis of 2-arylbenzothiazole derivatives in the presence of H$_3$PO$_4$/ZrO$_2$-TiO$_2$ (1/1)–CPB was investigated using different aldehydes and 2-aminothiophenol under mild conditions. In all cases, the reaction proceeded smoothly to give the corresponding products in high to excellent yields. According to the results of Table 2, it was observed that the reactions with aldehydes carrying electron-withdrawing groups gave the products in high yields and high purity. On the other hand, the aldehydes with electron-donating groups showed products with moderate yields. The related data are indicated in Table 2.

The application of H$_3$PO$_4$/ZrO$_2$-TiO$_2$ (1/1)–CPB as a catalyst in the present work gave higher yields and efficiencies and shorter reaction times for preparation of 2-(4-nitrophenyl)benzothiazole compared with the previously reported works using other catalysts.[35–37] For example, results from silica sulfuric acid and phenyliodonium bis (trifluoroacetate) (PIFA) in this reaction under harsh reaction conditions are comparable with this method under mild conditions at room temperature (Table 3, entry 1 vs. 2–4). Furthermore, advantages of the H$_3$PO$_4$/ZrO$_2$-TiO$_2$ (1/1)–CPB using as catalyst in this reaction are thermal and chemical

| Entry | Reaction condition                              | Time (min) | Yield (%) | Ref. |
|-------|------------------------------------------------|------------|-----------|------|
| 1     | H$_3$PO$_4$/ZrO$_2$-TiO$_2$ (1/1)–CPB solvent free, rt | 10         | 96        | Present work |
| 2     | Silica sulfuric acid, EtOH, reflux              | 120        | 90        | [36] |
| 3     | Silica sulfuric acid, MW                        | 7          | 94        | [35] |
| 4     | PIFA [phenyliodonium bis (trifluoroacetate)], EtOH, MW | 15         | 86        | [37] |

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![Scheme 2](image.png)

**Scheme 2.** Proposed reaction mechanism for the synthesis of 2-arylbenzothiazoles.
stability, non-flammability properties, recyclability, simplicity of product isolation, purification, mild reaction condition, excellent product yields, and short reaction times.

A plausible mechanism for the formation of 2-arylbenzothiazoles is presented in Scheme 2. As can be seen, in the first step, it was protonated the carbonyl group of aldehyde by the catalyst, followed the nucleophilic attack by the amino group to produce an imine bond, then cyclized by treatment of the sulfur group with the imine bond. Finally, the intermediate is oxidized in air to form the target product.

In the view of industrial purposes, the reusability of the catalyst was investigated by carrying out repeated runs of the reaction on the same batch of the catalyst in the model reaction (Fig. 5). In order to regenerate the catalyst, after each cycle, it was separated and washed several times with ethyl acetate and acetone. Then, it was dried in oven at 90 °C, calcined at 550 °C for 4 h, and used in the subsequent run. The results showed that this catalyst can be reused five times with 15% loss in activity performance under solvent-free conditions at room temperature. Moreover, the SEM image of recycled catalyst after fifth run was provided (Fig. 6) that indicated any change in the structure of the catalyst after the reactions.
Experimental

Materials and methods

Chemicals were purchased from the Merck, Fluka, and Aldrich Chemical Companies in high purity. All of the materials were of commercial reagent grade. The aromatic aldehydes and o-aminothiophenol were purified by standard procedures.

The FT-IR spectra were obtained with potassium bromide pellets in the range 400–4000 cm\(^{-1}\) with a Perkin-Elmer 550 spectrometer. Melting points were determined in open capillaries using an Electro thermal MK3 apparatus and are uncorrected. The SEM image was recorded by a SERON (AIS-2100) scanning electron microscopy. All \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 MHz. The NMR spectra were obtained in CDCl\(_3\) solutions and are reported as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. The abbreviations used are singlet(s), doublet (d), triplet (t), and multiplet (m). Mass spectra were recorded on an Agilent Technology (HP) MS model 5973 Network Mass Selective Detector in electron impact (EI) ionization mode with an ionization voltage of 70 eV. The completion of the reaction was monitored by thin-layer chromatography (TLC) on silica-gel polygram SILG/UV 254 plates (from Merck Company).

General procedure for preparation of the catalyst

TiO\(_2\)-ZrO\(_2\) (1/1) was used as the support, which was prepared by the sol-gel method.\(^{[31,32]}\) Zirconium(IV) isopropoxide (70% wt. solution in 2-propanol) and titanium(IV) n-butoxide (99%) were used as the precursors, and 2,4-pentandione (H-acac) was used as the complexing agent. Appropriate amounts of zirconium propoxide and titanium n-butoxide were dissolved in the solvent, n-butanol. The solution was heated to 60°C. The components were thoroughly mixed. Then the solution was cooled down to room temperature, and H-acac as the complexing agent was added. Then the clear solution was hydrolyzed with deionized water containing cetyl pyridinium bromide (CPB) surfactant (mol surfactant/mol alkoxide = 0.1). The solutions were left overnight to hydrolyze the alkoxides, yielding transparent gels. The transparent gels were dried at 110°C to remove water and solvent, and then calcined at 500°C for 5 h to remove the organics. The support was denoted as ZrO\(_2\)-TiO\(_2\) (1/1)–CPB. Then a series of catalysts with varying H\(_3\)PO\(_4\) contents were prepared by impregnating calculated amounts of H\(_3\)PO\(_4\) dissolved in deionized water on the TiO\(_2\)-ZrO\(_2\) (1/1)–CPB support. The impregnated catalysts were dried at 110°C for 12 h and then calcined in air at 500°C for 6 h\(^{[30,33]}\)

General procedure for the synthesis of 2-arylbenzothiazoles catalyzed by H\(_3\)PO\(_4\)/TiO\(_2\)-ZrO\(_2\) (1/1)

A mixture of 2-aminothiophenol (1 mmol, 0.995 g), aldehyde (1 mmol), and H\(_3\)PO\(_4\)-TiO\(_2\)-ZrO\(_2\) (1/1) (40 mg, 30 wt% H\(_3\)PO\(_4\)) were added in a beaker and the reaction mixture was mixed properly with the help of glass rod under solvent-free condition at room temperature. The progress of the reaction was monitored by TLC (ethylacetate–hexane, 4:6). After completion of the reaction, the reaction mixture was dispersed in ethyl acetate (5 mL) and filtered and the catalyst was washed several times with ethyl acetate and
acetone. Then, the filtrate was evaporated under reduced pressure to isolate a solid residue and recrystallized from hot ethanol (10 mL) to afford the corresponding products. All of the 2-arylbenzothiazole products were characterized by IR, $^1$H NMR, $^{13}$C NMR, and mass spectroscopy and identified by comparison of their physical and spectral data with those of authentic samples.\[^{34,35}\]

**2-phenyl-benzothiazole**

White solid; mp $= 110–112 \, ^\circ C$ (mp $= 111–112 \, ^\circ C$)\[^{34}\]; IR (KBr)/$\nu$ (cm$^{-1}$): 3066, 3017, 2835, 1608, 1587, 1476,1430, 1476,1430, 830, 763; $^1$H NMR (400 MHz, CDCl$_3$) / $\delta$ ppm: 7.02–7.06 (t, 1H, $J = 7.6 \, Hz$, Ar-H), 7.25 (t, 1H, $J = 8.4 \, Hz$, Ar-H), 7.56–7.70 (m, 5H, Ar-H), 7.93 (d, 1H, $J = 7.6 \, Hz$, Ar-H), 8.41 (d, 1H, $J = 8.4 \, Hz$, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$) / $\delta$ ppm: 121.5, 123.4, 125.1, 126.4, 127.6, 128.9, 130.8, 133.9, 135.1, 155.1, 168.0; MS (EI, $m/z$): 211 (M$^+$, 42), 197 (8), 182 (40), 171 (6), 143 (11.9), 125 (100), 108 (18), 87 (83), 79 (44), 69 (9.4), 58 (70), 47(51).

**Conclusion**

In summary, a simple and mild procedure for the synthesis of 2-arylbenzothiazoles has been reported using the condensation reaction of 2-aminothiophenol and aromatic aldehydes over H$_3$PO$_4$/ZrO$_2$-TiO$_2$(1/1)–CPB as an efficient, ecofriendly, and recoverable heterogeneous catalyst. Mild conditions, high yields, short reaction times, and easy reaction workup procedure are the main advantages of this synthetic protocol.

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