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Zirconium(IV) Oxide Chloride and Anhydrous Copper(II) Sulfate Mediated Synthesis of 2-Substituted Benzothiazoles

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ABSTRACT: *A simple, fast and efficient benign procedure has been developed for one-pot synthesis of 2-substituted benzothiazoles in the presence of zirconium(IV) oxide chloride octahydrate ($ZrOCl_2 \cdot 8H_2O$) and anhydrous copper(II) sulfate. The reaction of 2-aminothiophenol with aldehydes and anhydrides was carried out efficiently in solvent-free conditions with or without microwave irradiation, and adducts were produced in good to excellent yields.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:136–141, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20191

INTRODUCTION

Benzothiazole and their derivatives are very important group of heterocyclic bicyclic systems [1], which play a fundamental role in organic and bioorganic chemistry. Because of their potent antitumor activity [2–5] and other important pharmaceutical utilities [6–9] such as their applications for treatment of autoimmune and inflammatory diseases, prevention of solid organ transplant rejection, epilepsy, analgesia, viral infections, cancer, and tuberculosis [10–16], there is significant interest in the synthesis of these compounds in recent years [17]. Also, they can be used in industry as antioxidants and vulcanization accelerators that highlight their synthesis necessity [18].

Organic and medicinal chemists are paying tremendous attention for the simplification or improvement of the existing methods that are widely used in the manufacture of pharmaceutical and industrial substances. Reactions under solid support, chemoenzymatic reactions, and microwave-induced reactions have already created an enormous impact in modern science. On the other hand, the development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.

In the literature, it is shown that there are few methods for the synthesis of benzothiazoles. The important ones include the reaction of 2-aminothiophenol with the substituted aromatic aldeydes and carboxylic acids or its derivatives in polyphosphate ester [19], polyphosphoric acid [20], or a mixture of methane-sulfonic and phosphorous pentoxide [21]; radical cyclization of phenylthioformamides in the presence of potassium ferricyanide [22] or bromine [23]; Pd-catalyzed cyclization of 2-bromophenylthioformamides [24]; palladium-catalyzed reaction of aryl halides with 2-aminothiophenol in the presence of carbon monoxide [25]; reaction of copper(I) thiobenzoate and 2-iodoanilines [26]; and the action of selenoamides on 2-aminothiophenol [27]. Most of these protocols, however, suffer from drawbacks, namely harsh reaction condition, high thermal

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conditions, long reaction time, and the use of acid or base catalysts and toxic metallic compounds that result in waste streams.

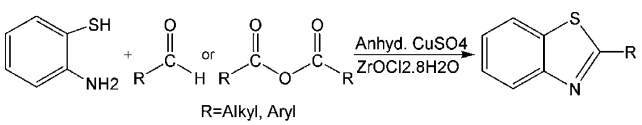
Microwave-assisted reactions in solvent-free condition have gained popularity because of rapid reaction rate, cleaner reaction, and ease of manipulation [28]. Recently, some methods use microwave heating for the synthesis of 2-substituted benzothiazoles such as condensation of aromatic or aliphatic aldehydes with 2-aminothiophenol on SiO_2 [29], aromatic aldehydes with 2-aminothiophenol in the presence of nitrobenzene/SiO_2 or nitrobenzene/montmorillonite K10 [30], aromatic aldehydes with 2-aminothiophenol in an ionic liquid [31], *ortho*-esters with 2-aminothiophenol using KFS clay [32], benzaldoximes or aromatic aldehydes with 2-aminothiophenol using $Ca(OCl)_2/Al_2O_3$ or MnO_2/SiO_2 [33], and Mn(III)-promoted cyclization of substituted thioformanilides [34].

Zirconium(IV) oxide chloride can function as a convenient medium as well as a Lewis acid in solvent and/or in solvent-free conditions [35]. Due to their availability and low toxicity, Zr(IV) salts have recently attracted much attention [36]. $ZrOCl_2 \cdot 8H_2O$ is a moisture stable, readily available, and inexpensive oxysalt of Zr and thus its handling is easier in comparison to that of the moisture-sensitive $ZrCl_4$. On the other hand, various copper salts were used extensively in organic synthesis and recently we have reported an efficient method for chemoselective dithioacetalization of aldehydes either in solvent and/or under solvent-free conditions using anhydrous copper sulfate [37].

Herein, we report an efficient, clean, fast, and mild method for the reaction of 2-aminothiophenol with various aldehydes and anhydrides in solvent-free conditions with or without microwave irradiation using anhydrous copper sulfate and zirconium(IV) oxide chloride separately (Scheme 1).

EXPERIMENTAL

The compounds gave all satisfactory spectroscopic data. IR spectra were taken as thin films for liquid compounds and as KBr pellets for solids on a Nicolet spectrometer (Magna 550). A Bruker (DRX-500 Avance) NMR was used to record the ^1H NMR spectra. All NMR spectra were determined in $CDCl_3$ and DMSO-d_6 at ambient temperature. The microwave oven used for this work was ETHOS-MR (800 W, 120°C) at 2450 MHz. Melting points were determined on a Buchi B540 apparatus.



SCHEME 1 General reaction.

General Procedure for the Synthesis of 2-Substituted Benzothiazole Compounds in Solvent-Free Condition

A mixture of 2-aminothiophenol (1 mmol), aromatic aldehyde (1 mmol), and catalytic amount of zirconium(IV) oxide chloride octahydrate (10^{-3} mmol) was stirred at 70°C (see Table 1) for appropriate time as required for completion of the reaction, which was monitored by TLC. The mixture was chromatographed over silica gel or PTLC using petroleum ether: ethyl acetate (4:1) to afford the pure product.

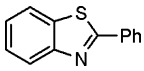
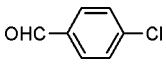
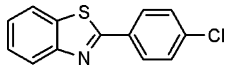
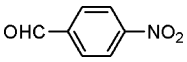
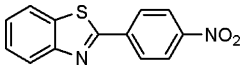
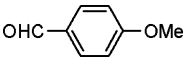
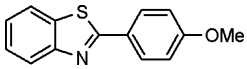
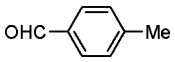
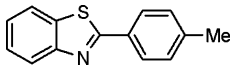
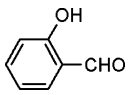
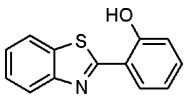
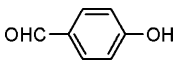
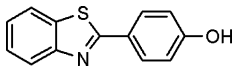
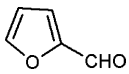
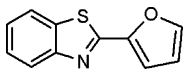
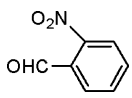
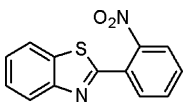
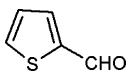
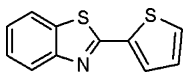
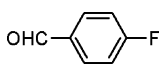
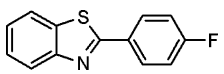
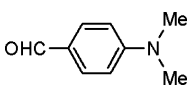
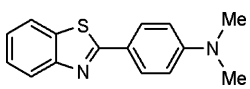
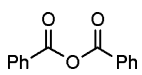
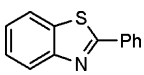
General Procedure for the Synthesis of 2-Substituted Benzothiazole Compounds in Microwave-Assisted Solvent-Free Condition

A mixture of 2-aminophenol (1 mmol), aldehyde or anhydride (1 mmol), and anhydrous copper sulfate(II) (0.6 g) or catalytic amount of zirconium(IV) oxide chloride octahydrate (10^{-3} mmol) was placed in a Teflon flask (~20 mL) and subjected to microwave irradiation for appropriate time (see Tables 1 and 2). The reaction mixture was chromatographed over silica gel or PTLC using petroleum ether:ethyl acetate (4:1) to afford the pure product.

RESULTS AND DISCUSSION

Our investigations showed that 2-aminothiophenol reacts smoothly with aldehydes and anhydrides in the presence of zirconium(IV) oxide chloride or anhydrous copper sulfate. The corresponding benzothiazoles were obtained in high to excellent yields. At first, we focused on zirconium(IV) oxide chloride as a catalyst in various conditions (solvent, solvent-free, and microwave irradiation). The best results were obtained in solvent-free conditions with or without microwave irradiation (see Table 3, entries 4 and 5). In a typical procedure, 2-aminothiophenol (1 mmol) with benzaldehyde (1 mmol) in the presence of a catalytic amount of $ZrOCl_2$ (10^{-3} mmol) at 70°C afforded the desired 2-substituted benzothiazole in 90% yield. Then the reaction was applied to a variety of aromatic aldehydes and anhydrides. The results are summarized in Table 1. Most of these reactions proceeded in relatively short times, and pure products were obtained by crystallization or PTLC.

TABLE 1 Synthesis of 2-Substituted Benzothiazoles Catalyzed by $ZrOCl_2 \cdot 8H_2O$ in Various Solvent-Free Conditions

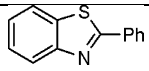
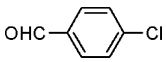
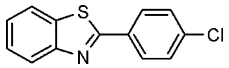
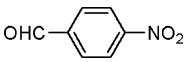
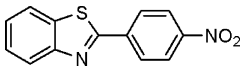
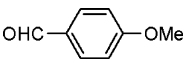
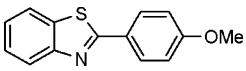
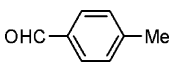
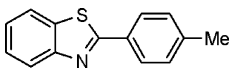
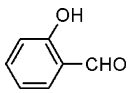
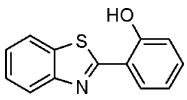
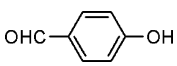
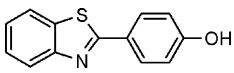
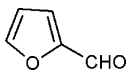
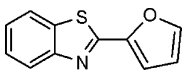
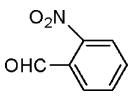
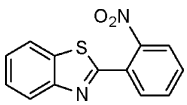
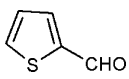
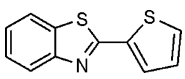
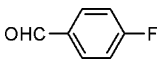
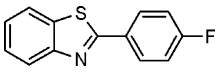
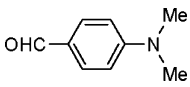
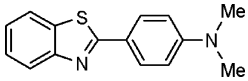
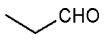
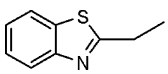
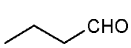
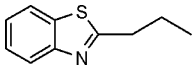
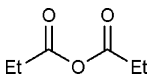
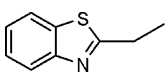
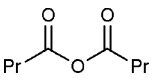
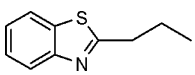
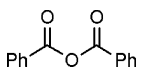
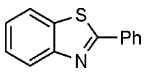
Entry	*Aldehyde or Anhydride*	*Product*	*Yield[a,b] (%)*	*Yield[a,c] (%)*
1	PhCHO		90	90 [31]
2			88	90 [31]
3			88	87 [31]
4			72	81 [31]
5			75	80 [29]
6			65	76 [31]
7			76	82 [31]
8			60	64 [31]
9			71	63 [29]
10			60	62 [31]
11			92	92 [34]
12			74	76 [8]
13			92	90

[a]All yields refer to isolated products and the products were characterized by mp, IR, ^{1}H-NMR, and their physical data were similar to those reported in the literature.
[b]The reactions were carried out at 70°C without microwave irradiation for 3 h.
[c]The reactions were carried out in microwave-assisted solvent-free condition for 4 min.

These reactions were also repeated in solvent-free conditions and under microwave irradiation. In this case similar yields were obtained in shorter reaction times.

Anhydrous copper sulfate as a good and cheap medium has also been used for this reaction. After optimization of the reaction conditions (solvent, solvent-free, and microwave irradiation), the best choice was found, microwave-assisted solvent-free conditions (see Table 3, entry 10). Aliphatic and aromatic aldehydes and anhydrides efficiently reacted with 2-aminothiophenol in the presence of

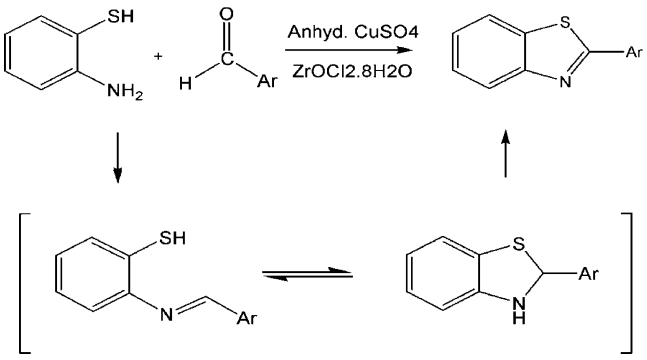
TABLE 2 Anhydrous Copper(II) Sulfate Mediated Synthesis of 2-Substituted Benzothiazoles from 2-Aminothiophenol under Microwave Irradiation

Entry	*Aldehyde or Anhydride*	*Product*	*Time (min)*	*Yield[a] (%)*
1	PhCHO		3	90
2			3	94
3			3	90
4			4	73
5			4	76
6			3	67
7			3	77
8			3	60
9			3	72
10			3	56
11			3	94
12			5	75
13			5	54 [29]
14			5	55 [29]
15			5	54
16			5	54
17			3	91

[a]All yields refer to isolated products and the products were characterized by mp, IR, ^{1}H-NMR, and their physical data were similar to those reported in the literature.

TABLE 3 Condensation of 2-Aminothiophenol and Benzaldehyde under Different Conditions

Entry	*Solvent*	*Condition*	*Lewis Acid*	*Time*	*Isolated Yield (%)*
1	EtOH	Reflux	Zirconium(IV) oxide chloride	3 h	85
2	CH_2Cl_2	Reflux	Zirconium(IV) oxide chloride	3 h	25
3	CH_3CN	Reflux	Zirconium(IV) oxide chloride	3 h	62
4	Solvent free	70°C	Zirconium(IV) oxide chloride	3 h	90
5	Solvent free	MW	Zirconium(IV) oxide chloride	3 min	90
6	EtOH	Reflux	Anhydrous copper(II) sulfate	3 h	84
7	CH_2Cl_2	Reflux	Anhydrous copper(II) sulfate	3 h	77
8	CH_3CN	Reflux	Anhydrous copper(II) sulfate	3 h	79
9	Solvent free	100°C	Anhydrous copper(II) sulfate	3 h	88
10	Solvent free	MW	Anhydrous copper(II) sulfate	3 min	90



SCHEME 2

anhydrous copper sulfate. The results are summarized in Table 2.

Aromatic aldehydes with electron-donating substituents and thiophene-2-carbaldehyde and furfural gave low yields (Tables 1 and 2, entries 4, 5, 7, 8, 10, and 12). The *ortho*-substituent on aromatic ring behaves in the same manner (Tables 1 and 2, entries 6 and 9). The reactivity of benzoic anhydride and benzaldehyde is similar in various examined conditions (Table 1, entries 1 and 13; Table 2, entries 1 and 17). Aliphatic aldehydes and anhydrides reacted with 2-aminothiophenol only in the presence of anhydrous copper sulfate and under microwave-assisted solvent-free conditions. The yields are relatively lower than aromatic aldehydes and anhydrides (Table 1, entries 13–16). A mechanism has been proposed for this type of transformation and is shown in Scheme 2.

CONCLUSION

In summary, anhydrous copper sulfate and zirconium(IV) oxide chloride octahydrate have been demonstrated to be a mild and efficient catalytic systems for the one-pot reaction of 2-aminothiophenol with a variety of aldehydes and anhydrides. Furthermore, the use of microwave irradiation considerably decreases the time of the reaction.

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