

# A Sustainable Approach for the Synthesis of Novel 2-Aminothiazoles Employing Zirconium Oxide as a Catalyst

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**Abstract:** *One-pot synthesis of 2-aminothiazoles employing ZrO<sub>2</sub> as a green catalyst and ethanol as a solvent was devised as an efficient method for synthesis a new series of thiazoles. First, a one-pot reaction of using substituted phenacyl bromide and substituted thiourea in 10 mol % ZrO<sub>2</sub>. This protocol has various feature such as a non-toxic solvent and an inexpensive, with rapid reaction times, high efficiency.*

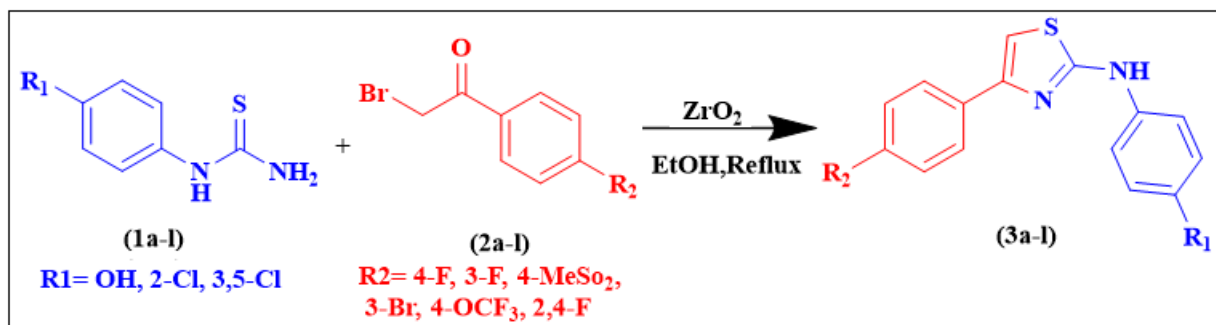
**Keywords:** 2-Aminothiazoles; Zirconium oxide; Green catalyst; One-pot synthesis; Hantzsch condensation; Heterogeneous catalysis; Sustainable chemistry

## 1. Introduction

Heterocyclic scaffolds are a prominent family of compounds that are important in numerous applications such as pharmacological, medicinal [1]. Early chemistry studies were primarily concerned with nitrogen and sulfur-containing heterocyclic compounds, they were intimately associated with the growth of organic chemistry, which examined substances separated from living things and is widely used as a structural theme in the search for new drugs [2]. Many bioactive compounds include heterocyclic systems with thiazole rings as a crucial structural element [3]. Numerous natural and synthetic chemicals include thiazoles, a family of significant scaffolds [4-7]. There are countless natural substances that include thiazole and its derivatives, including carboxylase, vitamin B1, thiostrepton, antibiotics and (penicillin) [8]. With great biological and medical significance. Thiazoles are widely used in medicinal chemistry and medication development to treat allergies, [9] bacterial infections, [10] swelling, [11] hypertension, [12] HIV, [13] Hypnotics, [14] such as schizophrenia [15] and antidepressant [16]. They exhibit significant biological activities like antimicrobial [17]. Antifungal [18], antitumor [19], anti-inflammatory [20], anticonvulsant [21], antitubercular [22]. Diuretic [23]. Neuroprotective and having antioxidant activity [24]. Aminothiazoles from the thiazole family may act as a pharmacophore. 2-Aminothiazole moieties are significant structural motifs in medicinal chemistry. as they exhibit anticancer properties [25]. Anti-prion drug [26]. Psychotropic drug [27]. Anti-

hypertensive [28]. Pesticidal [29]. Antiprotozoal activities [30] additionally,  $\alpha$ -halogenation of ketones is an important process in synthetic organic chemistry [31].

Due to of  $\alpha$ -bromoketones have significant reactivity and react with several nucleophiles, yielding a variety of physiologically active chemicals [32]. As active phases or supports, Metal oxides are one of the most significant and widely utilized forms of solid catalysts. Metal oxides are the most common type of catalyst in heterogeneous catalysis, and they are utilized for both redox and acid-base characteristics [33-36]. Zirconium dioxide ZrO<sub>2</sub> single oxides have outstanding catalytic qualities [37]. The most feasible way for synthesizing this family of compounds appears to be employing methyl carbonyl ( $\alpha$ -halo ketones) and thiourea as precursors (Hantzsch condensation) [38-39]. Modified Hantzsch one-pot condensation of active methylene ketones with thioureas has gained popularity due to their ability to be  $\alpha$ -halogenated in situ. This method saves time and costs in the synthesis of thiazoles. In situ  $\alpha$ -halogenation techniques employing different halogenating chemicals, such as Br<sub>2</sub>. [40]. I<sub>2</sub>, [41-44]. NBS [45-46] 1,3-dichloro 5,5-dimethylhydantoin [47]. It appears to be exciting to synthesize new thiazole derivatives containing a 2-Aminothiazole moiety. Herein, we report a one-pot synthesis of thiazole derivatives using the ZrO<sub>2</sub> as a catalyst. This approach not only simplifies the synthetic process but also bring into line with green chemistry principles (Scheme-1).

Scheme 1: Synthesis of 2-amino thiazole using ZrO<sub>2</sub>

## 2. Result and Discussion

Initially to investigate different parameters the synthesis of 2-amino thiazole, a model reaction using substituted phenyl thiourea (**1 mmol**) and substituted phenacyl bromide (**1 mmol**) was selected. The synthesis of 4-((4-(4-arylphenyl) thiazol-2-yl) amino) phenol has been investigated under various reaction conditions using various catalysts and solvents, and the results are shown in Table 1. Initially, the response was conducted in ethanol without a catalyst at both reflux and room temperature. Even after longer reaction times 12-14hrs, no product was formed in either case, representing that the reaction does not continue efficiently in the absence of a catalyst (Table 1 Entries 1 and 2).

The addition of metal oxide catalysts considerably improved the reaction outcome. When MgO<sub>2</sub>, CeO<sub>2</sub>, and TiO<sub>2</sub> were used in ethanol under reflux conditions Table 1 (Entries 3-5), the reaction progressed smoothly, and yielding the required product in low yields 62-68%. MgO<sub>2</sub> demonstrated slightly higher catalytic activity, yielding 68% in 170 min. This improvement is due to the acidic character of these metal oxides, which probably facilitates in cyclization and thiazole ring formation.

This we attribute to the acidic character of the metal oxides which we think also plays a role in cyclization and thiazole ring formation. Also we see that the use of vitamin B1 as a catalyst in (Table 1 Entry 6) did in fact improve the yield to 72% with a short reaction time (100 min). This we put forth that vitamin B1 does in fact play a role in nucleophilic activation and intermediate stabilization during the reaction. Of the studied catalysts ZrO<sub>2</sub> did very well. In (Table 1 Entry 7) we saw that ZrO<sub>2</sub> did in fact produce 74% yield at reflux in chloroform which we take as a sign of its great catalytic performance. To check the solvents' effect we looked at what various solvents did for the catalysts we had which is what we present in (Table 1 Entries 8-12). In water

(Table 1 Entry 8) we saw the lowest yield of 60% mostly due to reactants' poor solubility. In (Table 1 Entry 9) we saw moderate improvement which reported a 64% yield. When aprotic solvents were used we saw great variation. With dichloromethane DCM and DMF in (Table 1 Entries 10 and 11) we got yields of 58% and 76% respectively which DMF did better in which we put forward that it is due to its high polarity and ability to solvate reaction intermediates better. Also we saw that ethanol in the presence of ZrO<sub>2</sub> (Table 1 Entry 12) gave us the highest yield of 80% within just 10 min under reflux which we take as a result of the synergetic effect of ethanol as a protic solvent and ZrO<sub>2</sub> as a very good heterogeneous catalyst. As a whole it is found out that the type of catalyst and the. Ethanol in combination with ZrO<sub>2</sub> under reflux conditions was identified as the optimal system, offering advantages such as high yield, quick reaction times, ease of use, and safe reaction conditions for the environment.

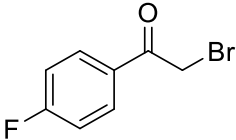
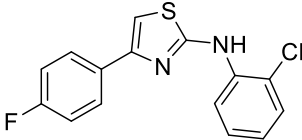
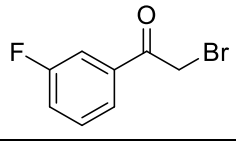
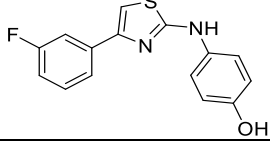
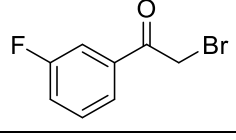
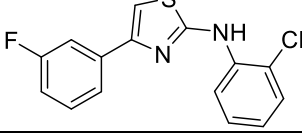
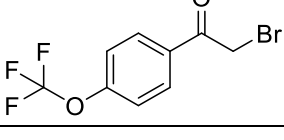
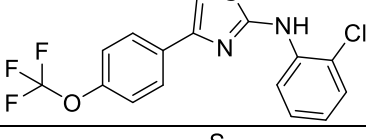
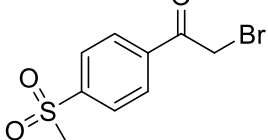
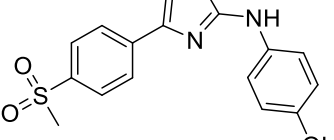
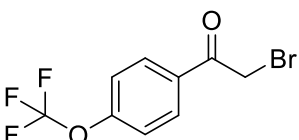
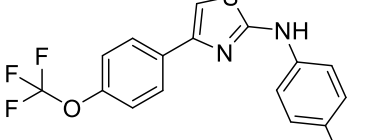
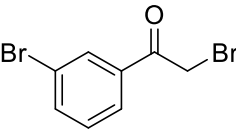
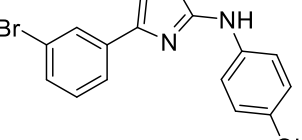
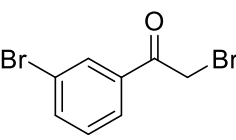
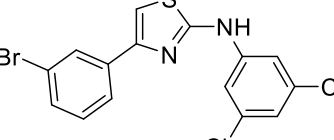
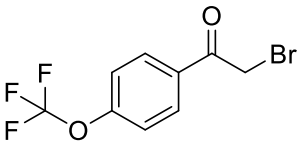
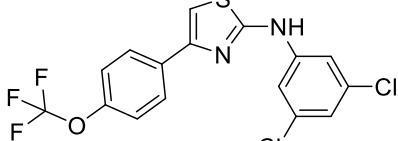
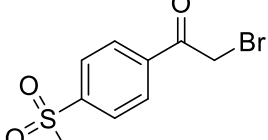
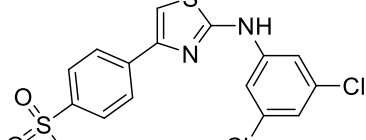
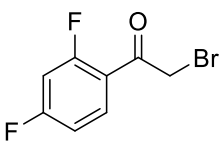
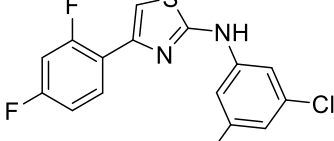
**Table 1:** Synthesis of 4-((4-(4-arylphenyl) thiazol-2-yl) amino) phenol using various catalysts and solvents.

Entry	Solvent	Catalyst	Condition	Time (Hrs/min)	Yield (%)
1	Ethanol	No catalyst	Reflux	14 hrs	-
2	Ethanol	No catalyst	R.T.	12 hrs	-
3	Ethanol	MgO <sub>2</sub>	Reflux	170	68
4	Ethanol	CeO <sub>2</sub>	Reflux	99	66
5	Ethanol	TiO <sub>2</sub>	Reflux	102	62
6	Ethanol	Vit B1	Reflux	100	72
7	CHCl <sub>3</sub>	ZrO <sub>2</sub>	Reflux	160	74
8	H <sub>2</sub> O	ZrO <sub>2</sub>	Reflux	110	76
9	EtOH/H <sub>2</sub> O	ZrO <sub>2</sub>	Reflux	80	60
10	DCM	ZrO <sub>2</sub>	Reflux	50	64
11	DMF	ZrO <sub>2</sub>	Reflux	42	58
12	Ethanol	ZrO <sub>2</sub>	Reflux	25	80

**Reaction conditions:** Compound substituted phenyl thiourea (1 mmol) and substituted phenacyl bromide's (1 mmol) with EtOH as a solvent at 78 °C.

**Table 2:** Preparation 4-((4-(4-arylphenyl) thiazol-2-yl) amino) phenol derivatives catalyzed by ZrO<sub>2</sub> at 78 °C temperature.

Entry	Phenacyl bromides	Product	Time (min)	Yield %	M.P. (oC)
1			10	80	122-124

2			12	72	112-114
3			11	78	114-116
4			13	76	130-132
5			14	84	98-100
6			16	82	102-104
7			17	86	104-106
8			21	83	117-119
9			20	74	88-90
10			14	75	94-96
11			12	70	108-110
12			18	77	125-127

Reaction conditions: mixture of substituted phenyl thiourea (1 mmol) and substituted phenacyl bromide's (1 mmol) with EtOH as a solvent at temperature 78 °C.

Optimized conditions were used to study the reaction using substituted phenacyl bromide with donate or withdraw electroning to offer 4-((4-(4-arylphenyl) thiazol-2-yl) amino) phenol derivatives in good yield.

### 3. Conclusion

In conclusion, the synthesis of 2-amino thiazol in ethanol is produced using a one-pot multicomponent process utilizing ZrO<sub>2</sub>. Numerous benefits of the current approach include provides high yields without chromatography, wide substrate compatibility, scalability, rapid reaction times, and clean reaction profile.

#### Experimental:

All solvents and chemicals were purchased from BLD pharma without any purification. A gas burner with open capillary tubes was used to determine the melting points. At Saif Chandigarh Punjab University, nuclear magnetic resonance was measured using an Advanced NEU 500 MHZ NMR instrument. In deuterated dimethylsulphoxide (DMSO-*d*6), <sup>1</sup>H NMR and <sup>13</sup>C-NMR were performed.

#### General procedure for the synthesis of 4-((4-(4-arylphenyl) thiazol-2-yl) amino) phenol:

substituted phenyl thiourea (1 mmol) and substituted phenacyl bromide's (1 mmol) were mixed with 5ml ethanol to 10 ml single neck round bottom flask, followed by 10 mol% of ZrO<sub>2</sub> and was left to stir at 78°C. TLC was used to track the reaction's progress. After the reaction's solids product was filtered with cold water. The crude product was refined by crystallization in hot ethanol, the other derivatives were prepared using similar method. Finally, all derivatives confirmed by spectroscopic aspects such as <sup>1</sup>H, <sup>13</sup>C NMR IR.

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