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# A Facile One Pot Microwave Synthesis Of 2-Amino-5- Aryl Thiazole By Using $NaHSO_4$-$SiO_2$ Heterogenous Catalyst In Dry Media.

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**ABSTRACT**

The new novel series of 2-amino-5-phenyl thiazole derivatives were occurred in the reaction between thiourea and various substituted ketones. The reactions were carried out in the microwave oven under solvent free condition. The completion of the reactions was checked by TLC. The structures of the compounds were characterized by FT-IR, $^1$H and $^{13}$C NMR and elemental analysis. Synthesized compound were checked by their drug ability by using Lipinski's rule.
**Keywords**: Thiourea, microwave, IR, NMR data, $NaHSO_4$-$SiO_2$.

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## INTRODUCTION

Research over the past 50 years has been focused on meeting medical needs to treat infectious disease caused by life threatening pathogens. In spite of the introduction of a variety of antibacterial agents in multiple unrelated drug classes, resistance continues to emerge. Much research has been carried out with the aim to discover the therapeutic values of thiazole derivatives. $N_{4-}$ substituted triazolyl derivatives [1] have found to posses anticonvulsant property whereas 4- thizolidone derivatives have show a very good antifungal activity. (1, 3 benzothiazol-2yl) amino 9-(10H) acridinone derivatives [2] have found to posses antileshmanial activity. 4- substituted methoxybenzoyl-aryl-thiazole [3] has been found to possess a very good anticancer activity. Benzothiazole ring made from thiazole ring fused with benzene ring. Thiazole ring is a five-member ring consists of the one nitrogen and one sulfur atom in the ring. Benzothiazoles are bicyclic ring system. In the 1950s, a number of 2-amino benzothiazoles were intensively studied as central muscale relaxants and found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments. 2- aminobenzothiazoloes are highly reactive compounds. They are extensively utilized as reactant or reaction intermediates since $NH_2$ and endocyclic N functions are suitably situated to enable reaction with common electrophillic agents to form a veriety of fused heterocyclic compounds [4]. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. Presence of hydrophobic moieties in molecule is conductive for cytotoxic activity of benzothiazole derivative against cell lines. The $NH_2$, -OH, -Cl group containing benzothiazole shows better anticancer activity [5]. Thiazole containing N=C=S moiety have been used as antiphychotics [6] and antimalarial [7] 2- Aminothiazole derivatives are well explored as useful clinical agents and some derivatives of thiazole have shown inhibition towards herpes simplex virus [8]. Some derivatives of 2- aminothiazoles bearing arylazo moiety at position-5 have shown good cytostatic activity [9].

In a Multi Component Reaction (MCR) more than two starting material reacts to give a product. There by most of the atoms of the starting material must be found in the product (atom economy). In pseudo MCR's, not all starting materials are highly variable. It is useful for the fast synthesis of a high number of compounds with wanted properties, in example drug discovery and catalysis research.

There is an increasing interest in the use of environmentally begin reagents and conditions [10], and particularly to solvent free procedures [11]. Avoiding organic solvents during the reaction in organic synthesis leads to clean, efficient and economical technology, safe is largely increased, work-up is considerably simplified, cost is reduced, and increased amounts of reactants can be used in the same equipment, reactivity and sometimes selectively are enhanced with dilution.

In this present work we can synthesis the new novel 2-amino-5-phenyl thiazole derivatives and they are well characterized by FT-IR and $^1$H and $^{13}$C NMR spectral studies and elemental analysis. The synthesized compounds were checked by their drug ability by using Lipinski's rule. The synthesis were carried out in two methods one is convectional and another one is microwave irradiation method and the yields are compared.

## EXPERIMENTAL

### Chemistry

The starting material, various acetophenones was purchased from sigma Aldrich. The TLC was checked by using the chloroform as the solvent. Melting points were carried out in an open capillary method and are uncorrected. FT-IR spectrum was recorded in a Schimadzu (1650) model instrument. Elemental analysis was carried out in a perkinelmer 240C model instrument. All the chemicals used for synthesis are of AR grade. Microwave oven (CEM Discover Benchmate., USA) was used for microwave assisted synthesis.

### General procedure for Synthesis of 2-amino-4-phenylthiazole

### Convectional method:

Substituted acetophenone (0.01m, 1.2ml), thiourea (0.01m) and iodine (0.01m) were dissolved in 30ml ethanol and refluxed for 8 hours in a heating mantle. The reaction was observed by using TLC. After completion of the reaction, the reaction got precipitated. It was filtered and dried to yield the product.

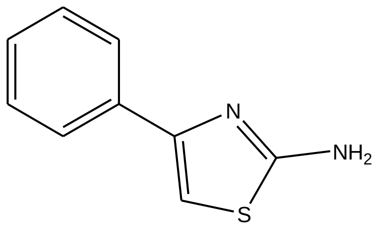
Recrystallization was carried out using ethanol as the solvent. The purity of the sample was tested by TLC using the solvent system petroleum ether and ethyl acetate in the ratio 8:2.

**Microwave method:**

Substituted acetophenone (0.01m, 1.2ml), thiourea (0.01m) and $NaHSO_4$ – $SiO_2$ heterogeneous catalysts are taken in the pestle and mortar and the mixture was grinding well for 2-3 minutes and the mixture is transferred in to 100ml beaker, then the mixture was irradiated for 10-15 minutes in microwave oven under the power of 320 w. The completion of the reactions was checked by TLC (Thin Layer Chromatography). After completion of the reaction, the reaction mixture was extracted with ethylacetate (3X 10 ml). The catalyst was removed by filtration and reused. After drying the ethylacetate extracts over anhydrous $MgSO_4$, the organic layer was concentrated *in vacuo* to furnish the products and recrystallized in methanol/ ethanol to afford pure products.

**RESULT AND DISCUSSION**

The utilizationof 2-amino-5-aryl thiazole (3a-f) through a series of chemical reactions (scheme-1) gave low molecular weight compounds. The substituted acetophenone, thiourea and $NaHSO_4$-$SiO_2$ catalyst was grinding well by using pestle and mortor. After the mixture was transferred in to 100 ml beaker and then it was irradiated for microwave oven for 10-15 minutes. The completion of the reaction was checked by TLC. The reaction was also carried out in a conventional method.The chemical structures of the compound were confirmed by FT-IR, $^1$H NMR, $^{13}$C NMR and elemental analysis. The representative compound 2-amino -5-phenyl thiozole shows that the FT-IR spectra presented absorption band for $NH_2$ at 3,446.79 cm$^{-1}$. And for the C=C at 1671.35 cm$^{-1}$. The bands at 1579.70 and 686 cm$^{-1}$ are due to C=N and C-S-C respectively. Absorption bands determined by vibrations of the aromatic ring appeared at 3084.18 and 3007.02 cm$^{-1}$. The absorption at1074.35 cm$^{-1}$ are due to the presence of N=C-S-C=. The aromatic ring stretching appeared at 823.60, 746.45, 713.00, 642.30 cm$^{-1}$. $^1$H NMR spectra certified the presence of structural elements characteristic of every compound. Therefore, the signal at 4 ppm is due to the presence of $NH_2$ proton. The signal at 6.62 ppm is due the presence of CH of thiazole ring proton. The aromatic protons appeared at in the range of 7.22-7.48 ppm. The $^{13}$C NMR spectra certified the presence of structural elements characteristic of every compound. The $^{13}$C resonance at 170.53 ppm is due the presence of C-2 carbon. The $^{13}$C resonance at 100.05 ppm is attributed to C-4 carbon. The resonance at 148.24 ppm is due the presence of C-5 carbon. The aromatic carbon appeared at in the range of 128.45-127.58 ppm. The remaining $^{13}$C resonance at 133.17 ppm is due to *ipso* carbon.the elemental composition was established by means of nitrogen and sulphur element analysis. The found nitrogen content, of 15.81 %, *vs*, the calculated value of 15.90 %, and of 18.23 %, *vs* the calculated value of 18.19 %, for the representative compound, indicated that the title compounds. From the above spectral studies the synthesized compounds were confirmed. The proposed structure of the synthesized compound is 2-amino-5-phenyl thiazole.




2-amino-5-phenylthiazole

**Lipinski's Rule:**

The above synthesized compounds obey the rule of five, because they have not (1). No more than 5 Hydrogen bond donors (the total number of Nitrogen-Hydrogen and Oxygen-Hydrogen bonds). (2). Not more than 10 Hydrogen bond acceptors (all Nitrogen and Oxygen atoms). (3). A molecular mass of our synthesized compounds not exceeding 500 Daltons.(Molecular mass of Compound 3a-176, Compound 3b-255, Compound 3c-190, Compound 3d-221, Compound 3e- 225, Compound 3f- 252). (4). Melting point of our synthesized compounds are not exceeding 500°C ( Melting point of Compound 3a-160°C, Compound 3b-54°C, Compound

3c- 58°C, Compound 3d- 128°C, Compound 3e- 190°C, Compound 3f- 110°C ).(5). The log p value also not exceeding greater than 5 (log p values of Compound 3a- 3.05, Compound 3b-3.88, Compound 3c-3.54, Compound 3d-2.92, Compound 3e- 4.05, Compound 3f- 4.72). So the above synthesized compounds are obeyed the Lipinski's Rule [12] of Five. Therefore our synthesized compounds 3a-f are drug molecules. The values are shown in Table 1.

**Table 1: Lipinski's Rule for Compound (3a-f)**

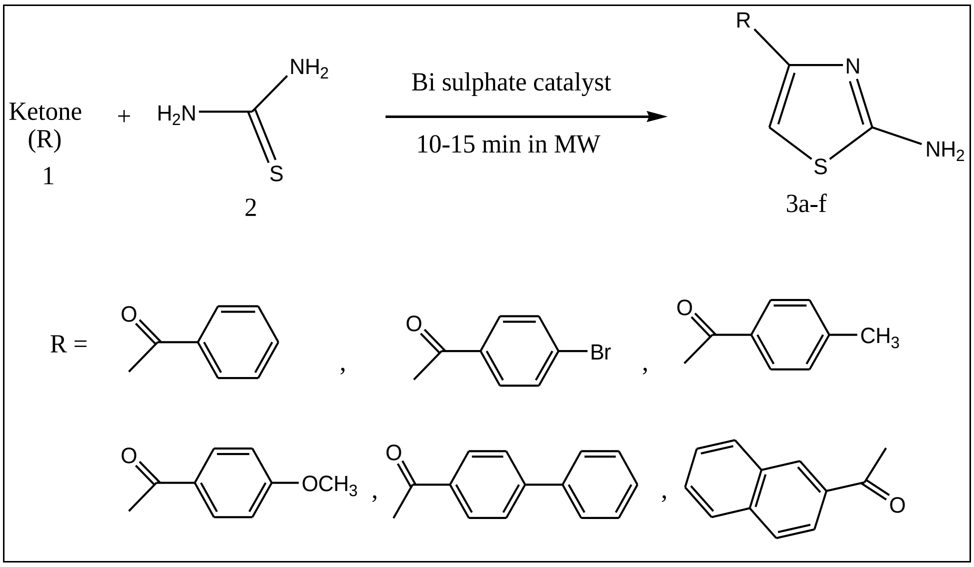
| Compound | No. of H-bond donors | No. of H-bond acceptors | Molecular mass m/z | Melting point in °C | log p |
|---|---|---|---|---|---|
| **3a** | <5 | <10 | 176 | 160 | 3.05 |
| **3b** | <5 | <10 | 255 | 54 | 3.88 |
| **3c** | <5 | <10 | 190 | 58 | 3.54 |
| **3d** | <5 | <10 | 221 | 128 | 2.92 |
| **3e** | <5 | <10 | 225 | 190 | 4.05 |
| **3f** | <5 | <10 | 252 | 110 | 4.72 |

**Comparison of Microwave irradiation method and Conventional methods of Compounds (3a-3f):**

All the synthesized compounds yields and reaction times were compared with both the methods, the synthetic yields are very high in microwave irradiation method when compared to conventional method and also the reaction times are very low in microwave irradiation method, so the microwave irradiation method is superior method when compared with the conventional methods. The yields and reaction times are shown in Table 2.

**Table 2: Comparison of Microwave and Conventional studies of Compounds (3a-3f)**

| Compound | R | Time Δ (h)/ minutes | | Yield % | |
|---|---|---|---|---|---|
| | | Conventional method (h) | Microwave irradiation method (minutes) | Conventional method | Microwave irradiation method |
| **3a** | H | 0.5 | 3 | 70 | 87 |
| **3b** | Br | 1 | 4 | 72 | 85 |
| **3c** | $CH_3$ | 1 | 4.3 | 65 | 75 |
| **3d** | $OCH_3$ | 1 | 6 | 60 | 72 |
| **3e** | Naphthalene | 1.5 | 4 | 81 | 90 |
| **3f** | Biphenyl | 1.5 | 4.45 | 78 | 81 |




**Scheme 1: Path way to synthesis of 2-amino-5- phenyl thiazole derivatives (3a-f)**

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**Synthesis of 2-amino-5-phenylthiazole (3a)**

Reaction time 3 min, m.p. 224.06$^0$C. IR: $\nu_{max}$ (KBr, $cm^{-1}$): 3,334.92 ($NH_2$), 1670.35 (C=C), 1579.70 (C=N), 686 (C-S-C), 3199.91, 3161.33, 3120.82 (Aromatic CH), 826.60, 736.45, 713.0, 643.3 (Aromatic ring stretching), 1076.35 (N=C-S-C=). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 4.00(2H, $NH_2$), 6.62 (CH in thiazole ring), 7.22 – 7.48 (Aromatic protons). $^{13}$C NMR (200 MHz, DMSO-$d_6$) δ: 170.5 (C-2), 100.0 (C-4), 148.2 (C-5), 133.1-127.5 (phenyl carbons). Molecular formula: $C_9H_8N_2S$. Molecular Weight: 176, Anal. Calcd. for $C_9H_8N_2S$: C-61.34; H-4.58; N-15.90; S-18.19%. Found: C-61.36; H-4.50; N- 15.81; S-18.23%.

**Synthesis of 2-amino-5(-4-bromo) phenyl Thiazole (3b)**

Reaction time 4 min, m.p. 296.38$^0$C. IR: $\nu_{max}$ (KBr, $cm^{-1}$): 3,446.79 ($NH_2$), 1671.35 (C=C), 1579.70 (C=N), 686 (C-S-C), 3084.18, 3007.02 (Aromatic CH), 823.60, 746.45, 713.0, 642.3 (Aromatic ring stretching), 1074.35 (N=C-S-C=). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 4.00(2H, $NH_2$), 6.6 (CH in thiazole ring), 7.37, 7.49 (Aromatic protons). $^{13}$C NMR (200 MHz, DMSO-$d_6$) δ: 170.5 (C-2), 100.0 (C-4), 148.2 (C-5), 138.4-130.1 (phenyl carbons). Molecular formula: $C_9H_7N_2SBr$. Molecular Weight: 225, Anal. Calcd. for $C_9H_7N_2SBr$: C-42.37; H- 2.77; N-10.98; S-12.57, Br- 31.32%. Found: C-42.27; H- 2.71; N- 10.92; S-12.53, Br – 31.28%.

**Synthesis of 2-amino-5(4-methyl) phenyl Thiazole(3c)**

Reaction time 4 min 30 sec, m.p. 247$^0$C. IR: $\nu_{max}$ (KBr, $cm^{-1}$): 3,398.57 ($NH_2$), 1614.42 (C=C), 1458.18 (C=N), 626.67 (C-S-C), 3174.63 (Aromatic CH), 725.23 (Aromatic ring stretching), 1080.14 (N=C-S-C=). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 4.00(2H, $NH_2$), 6.6 (CH in thiazole ring), 7.12, 7.36 (Aromatic protons), 2.35 (phenyl ring $CH_3$). $^{13}$C NMR (200 MHz, DMSO-$d_6$) δ: 170.5 (C-2), 100.0 (C-4), 148.2 (C-5), 138.4, 129.6, 127.4 (phenyl carbons), 24.3 (methyl group C). Molecular formula: $C_{10}H_{10}N_2S$. Molecular Weight: 190 Anal. Calcd. For $C_{10}H_{10}N_2S$: C-63.13; H- 5.30; N-14.72; S-16.85%. Found: C- 63.11; H- 5.25; N- 14.68; S-16.79%.

**Synthesis of 2-amino-5(-4-methoxy) phenyl Thiazole (3d)**

Reaction time 6 min, m.p. 270.08$^0$C. IR: $\nu_{max}$ (KBr, $cm^{-1}$): 3,332.99 ($NH_2$), 1674.21 (C=C), 1593.13 (C=N), 677.01 (C-S-C), 3061.03, 2983.88, 2953.02 (Aromatic CH), 829.39, 742.59, 651.94 (Aromatic ring stretching), 1024.20 (N=C-S-C=). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 4.00(2H, $NH_2$), 6.6 (CH in thiazole ring), 7.37, 6.83 (Aromatic protons), 3.73 ($OCH_3$ at phenyl ring). $^{13}$C NMR (200 MHz, DMSO-$d_6$) δ: 170.5 (C-2), 100.0 (C-4), 148.2 (C-5), 128.5, 125.4, 114.8 (phenyl carbons), 160.7 (-C-$OCH_3$), 55.9 (C at $OCH_3$ group). Molecular formula: $C_{11}H_{13}ON_2S$. Molecular Weight: 221 Anal. Calcd. For $C_{11}H_{13}ON_2S$: C-58.23; H- 4.89; N-13.58; S-15.55; O – 7.76%. Found: C- 58.18; H- 4.90; N- 13.51; S-15.59; O- 7.73 %.

**Synthesis of 4-(naphthalene-2-yl) Thiazole-2-amine (3e)**

Reaction time 4 min, m.p. 314.36$^0$C. IR: $\nu_{max}$ (KBr, $cm^{-1}$): 3,329.14 ($NH_2$), 1672.28 (C=C), 1535.34 (C=N), 663.51 (C-S-C), 3118.90, 3055.24, 2991.59 (Aromatic CH), 842.89, 827.46, 756.10, 711.73 (Aromatic ring stretching), 1076.28 (N=C-S-C=). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 4.00(2H, $NH_2$), 6.6 (CH in thiazole ring), 7.89, 7.54, 7.73, 7.67, 7.32 (Aromatic protons at naphthalene ring). $^{13}$C NMR (200 MHz, DMSO-$d_6$) δ: 170.5 (C-2), 100.0 (C-4), 148.2 (C-5), 133.1, 127.5, 129.3, 128.8 (phenyl carbons). Molecular formula: $C_{13}H_9N_2S$. Molecular Weight: 225, Anal. Calcd. For $C_{13}H_9N_2S$: C-69.00; H- 4.45; N-12.38; S-14.17%. Found: C- 58.98; H- 4.49; N-12.31; S-14.20 %.

**Synthesis of 2-amino-5-(-4-phenyl) biphenyl Thiazole (3f)**

Reaction time 4min 45 sec, m.p. 330.62$^0$C. IR: $\nu_{max}$ (KBr, $cm^{-1}$): 3,431.36, 3340.71 ($NH_2$), 1678.07 (C=C), 1598.99 (C=N), 686.66 (C-S-C), 3190.26, 3070.68, 2997.38 (Aromatic CH), 839.03, 763.81, 723.31, 640.37 (Aromatic ring stretching), 1078.21 (N=C-S-C=). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 4.00(2H, $NH_2$), 6.6 (CH in thiazole ring), 7.54, 7.48, 7.32, 7.22 (Aromatic protons at biphenyl ring). $^{13}$C NMR (200 MHz, DMSO-$d_6$) δ: 170.5 (C-2), 160.0 (C-4), 148.2 (C-5), 132.0, 128.0, 128.4, 136.5, 127.9, 129.3, 127.7 (biphenyl ring carbons). Molecular formula: $C_{15}H_{12}N_2S$. Molecular Weight: 252, Anal. Calcd. For $C_{15}H_{12}N_2S$: C-71.40; H- 4.79; N-11.10; S-12.71%. Found: C- 71.45; H- 4.71; N- 11.09; S-12.68 %.

**Recover and Reuse of the Catalyst:**

The catalyst was reused by washed with acetone, filtered dried and activated**.** Up to five to six times the catalyst were collected and reused. Compared with up to five runs the yields are more or less similar in rate. There is no wide change in the yield of the synthesized compounds (3a-f). The comparison is given in graphically ie Fig 1.

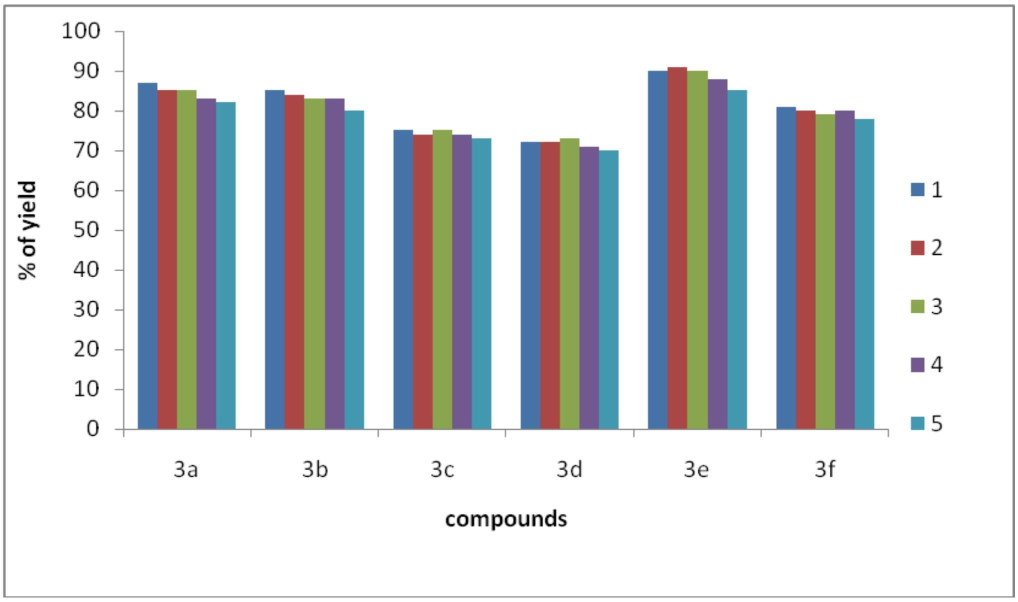


**Figure 1: Recovery and reuse of the heterogeneous catalyst $NaHSO_4$-$SiO_2$.**

## CONCLUSION

It has been demonstrated that activated $NaHSO_4$-$SiO_2$ is a highly effective and reusable catalyst for a synthesis of 5-substituted amino thiazole derivatives in "dry media". All synthesiszed compounds are characterized by their physical and analytical characterization including melting point, elemental analysis, FT-IR, NMR ($^1$H and $^{13}$C). This novel catalyst provides a clean and convenient alternative methodology for title compounds. This method not only offers the higher yield over conventional method but also eliminates the usage of the solvents such as ethanol, chloroform, ethyl acetate and also corrosive bases like NaOH. This reaction may have wide applicability and simple to synthesis the various variety of amino thiazoles synthon, which has two main groups i.e. thio, amine. The synthesized compounds are obeyed the drug ability of the Lipinski's Rule of Five.

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