ISSN: 2277-5536 (Print); 2277-5641 (Online)

MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED 2-AMINOTHIAZOLES

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ABSTRACT
A series of substituted 2-aminothiazoles (AT-1 to AT-4) have been synthesized by reacting substituted acetophenones, iodine and thiourea under microwave irradiation as green chemistry approach. The reactions proceed selectively and within a couple of minutes giving high yields of the products. The compounds were characterized by spectral (UV-visible, IR, NMR and GC-MS) and thermal analyses. The TG curves of compounds were analyzed to calculate various kinetic parameters (n, E, Z, ΔS and G) using Coats – Redfern (C.R.), MacCallum-Tanner (M.T.) and Horowitz-Metzger (H.M.) method. The compounds were tested for antibacterial activity against *B. subtilis* and *E. coli* and antifungal activity against *A. niger* and *C. albicans* using serial dilution technique.

KEY WORDS: Aminothiazoles, antibacterial and antifungal activity, Green chemistry, Microwave mediated synthesis, Thermal analysis.

INTRODUCTION

Microwave (MW) mediated synthesis has played an important role in organic synthesis over the last decade (Lidstrom, 2001; Nilsson, 2006). Seipel *et. al.* (2008) reported that the MW assisted reaction times are eighty times faster than the conventional heating reaction times and these reactions are more energy efficient than those which use conventional heating. MW heating provides better heating efficiency, high rate of reaction, energy and better quality products and therefore it is of interest to use MW mediated reactions in organic synthesis.

Thiazoles are well known as biological active compounds. They exhibit a wide range of antibacterial and antifungal (Ulusoy, 2002; Kaplancikli, 2004), anti-HIV (Al-Saddi, 2008), hypertension (Tripathi, 2003), anti-inflammatory (Karpov, 2001), anticancer (Baselt, 2008), and anti-convulsant (Karade, 2008) activities. Disubstituted thiazoles posses anti-inflammatory and analgesic (Hadjipavlou, 1993) activities. Among thiazoles, 2- aminothiazoles have attracted the attention of researchers because they form Schiff bases with aldehydes. Schiff bases possess strong ability to form metal complexes (Syamal, 1989; Yamada, 1999). MW synthesis of aminothiazoles is of interest in view of green chemistry approach. Kabalka and Mereddy (2006) reported MW promoted synthesis of 2-(N-substituted) aminothiazoles from α-bromoketones. Khrustalev et.al.(2008) reported synthesis of 2-amino-4-phenylthiazole under MW irradiation. In the present communication, we are reporting the MW mediated synthesis of substituted 2-aminothiazoles (AT-1 to AT-4) (*Fig.1*) by reacting substituted acetophenones, iodine and thiourea under microwave irradiation. The products were identified by spectral (Uv-visible, IR, NMR and GC-MS) analysis.

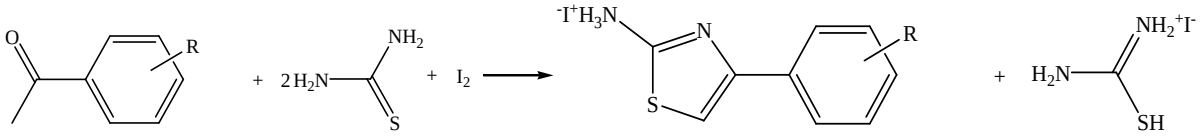

Figure 1. AT-1: 4-(*p*-bromophenyl)-2-aminothiazole (R= *p*-Br), AT-2: 4-(*p*-fluorophenyl)-2-aminothiazole (R= *p*-F), AT-3: 4-(*o*-hyroxyphenyl)-2-aminothiazole (R= *o*-OH) and AT-4: 4-(*o, p*-dichlorophenyl)-2-aminothiazole (R= *o.p*-Cl_2).

MATERIALS AND METHODS

Instrumentation

Uv-visible spectra were recorded in ethanol on Shimadzu A 600Uv-visible spectrometer. IR spectra were recorded in KBr pellets on Shimadzu FT-IR 8400 spectrometer. H^1NMR spectra were recorded in $CDCl_3$ using TMS as the standard on Varian 300MHz spectrometer. GC-MS were recorded on Shimadzu GC-MS QP 5050 mass spectrometer. Thermogram was recorded on V2 4F TA thermal analyzer at the heating rate 1^oC per minute in nitrogen atmosphere. Microwave mediated reaction was carried out in conventional 25 DLX microwave oven.
All reagents used such as substituted acetophenones, thiourea and Iodine were pure AR grade. Solvents such as ethanol and diethyl ether were purified prior to use as per standard procedure.

Synthesis of 4-(substituted phenyl)-2-aminothiazole

A 4-(substituted phenyl)-2-aminothiazole was synthesized by using the method reported by Khrustalev (2008). A mixture of substituted acetophenone (1mmol), thiourea (2mmol) and iodine (1mmol) was stirred well and exposed to microwave irradiations for five minute with 30 sec. pause at different watt required for each substituted 2-aminothuiazoles (Table 1). Then 100 ml distilled water was added and exposed to microwave irradiation at 180 W for 5-6 minute with 1 minute pause till the precipitate dissolve. The yellow solution was filtered. The filtrate was made alkaline by the addition of ammonia solution to separate out product. The product was recrystillised in ethyl alcohol and washed with diethyl ether and dried under vacuum. The purity of compound was tested with TLC.

Antibacterial and antifungal activity

Antibacterial and antifungal activities of (AT-1 to AT-4) were tested by serial dilution technique (Spooner, 1972). Eight test tubes containing 5 ml of sterile nutrient / sabouraud broth were inoculated with 0.02ml of 24 h old culture of bacteria *S. aureus* and *K. pneumoniae* and fungi *A. niger* and *C. albicans* respectively. Different amount of (AT-1 to AT-4) in ethanol were aseptically added with the help of sterile pipettes from the stock solution 200 µg/ml to 5 ml quantities of respective media so as to reach the concentration from 1µg/ml to 50µg/ml. All test tubes were inoculated at 37^0C and at room temperature for bacteria and fungi respectively. Test tubes inoculated with organism were observed for presence of turbidity after 24h and 48h respectively. The lowest concentration of (AT-1 to AT-4) inhibiting the growth of organism were determined as MIC value.

RESULTS AND DISCUSSION

Substituted 2-aminothiazoles (AT-1 to AT-4) were synthesized by reacting substituted acetophenones, iodine and thiourea using the conventional method (Das, 1955). The reaction requires around 20 hrs conventional heating. The yields of the products and heating times are shown in Table 1.

Table 1. Synthesis of 4-aryl-2-aminothiazole

Sr. No.	Compound	Conventional method of synthesis[12]		MW mediated synthesis			Melting point (^{0}C)
		Yield (%)	Heating time(h)	Yield (%)	Heating time(min.)	Input power (Watt)	
1	AT-1	50	20	75	5	360	176
2	AT-2	75	20	90	5	270	112
3	AT-3	30	20	65	5	270	139
4	AT-4	48	20	62	5	540	158

Table 2. Kinetic parameters estimated by Coats – Redfern (C.R.), MacCallum-Tanner (M.T.) and Horowitz-Metzger (H.M.) method.

Kinetic parameters	Stage – I of AT-4		
	C.R.	M.T.	H.M.
n	0.47	0.45	0.75
E	21.507	21.329	26.826
Z	$3.83x10^6$	$6.20x10^{12}$	$9.36x10^{11}$
ΔS	-15.15	-0.8514	-2.44
G	24.032	22.4715	27.128
Units: E (kcal mol^{-1}), Z (S^{-1}), ΔS ($JK^{-1}mol^{-1}$), G (kcal mol^{-1})			

Now we reported synthesis of AT-1 to AT-4 by reacting substituted acetophenones, iodine and thiourea under MW irradiation. The MW irradiated reactions were completed in a couple of minutes (~ 5 min) giving good yields of expected products (*Table 1*). We found that MW mediated synthesis of substituted 2-aminothiazoles is 200 times faster than the conventional method of synthesis (Das, 1955). The compounds AT-1 to AT-4 are colourless crystalline solids having sharp melting points and soluble in common organic solvents. Physical constant data is given in *Table 1.* The compounds gave satisfactory elemental (C, H and N) and spectral ((Uv-visible, IR, NMR and GC-MS) data. The mass spectrum of each compound shows the molecular ion M^+ peak corresponding to the molecular weight of the compound and thus confirms the molecular formula.

AT-1: Uv-visible: λ_{max} 310 nm; GC-MS: m/z (relative intensity %):254/256* (100/100*) (M^+ peak) (Molecular formula: $C_9H_7BrN_2S$), 212/214* (28/30*), 133 (25), 89 (28).

AT-2: Uv-visible: λ_{max} 303nm; IR : ν(NH_2)- ~3314cm^{-1}, ν(C=N)- ~1627cm^{-1} and ν(C-S-C)- ~585cm^{-1} ; H^1NMR: ($CDCl_3$, TMS, δppm) 5.3 (2H, s, NH_2), 7.7 (2H, m, Ar-H), 7.0 (2H, t, Ar-H), 6.6 (1H, s, H-thiazole); GC-MS: m/z (relative intensity %): 194 (100) (M^+ peak) (Molecular formula: $C_9H_7FN_2S$), 152 (81.5), 122 (14.8), 108 (22.2), 107 (24), 95 (5.6), 75 (8.33), 57 (9.26), 50 (3.7).

AT-3: Uv-visible: λ_{max} 300nm; IR : ν(NH_2)- ~3340cm^{-1}, ν(C=N)- ~1620cm^{-1} and ν(C-S-C)- ~550cm^{-1}, ν(OH)- ~3460cm^{-1}; H^1NMR: ($CDCl_3$, TMS, δppm) 5.01 (2H, s, NH_2), 6.8-6.9 (5H, m, Ar-H and H-thiazole), 11.52 (1H, s, -OH); GC-MS: m/z (relative intensity %): 192 (100) (M^+ peak) (Molecular formula: $C_9H_8ON_2S$), 150 (34), 133 (48), 121 (41), 104 (33), 90 (16), 77 (21), 69(21).

AT-4: Uv-visible: λ_{max} 300nm; IR**:** ν(NH_2)- ~3440cm^{-1}, ν(C=N)- ~1610cm^{-1} and ν(C-S-C)- ~556cm^{-1}; H^1NMR: ($CDCl_3$, TMS, δppm) 5.05 (2H, s, NH_2), 7.05 (1H, s, H-thiazole), 7.4 (2H, d, Ar-H), 7.85 (1H, s, Ar-H); GC-MS: m/z (relative intensity %): 244/246*/248* (100/66.67*/15.15*) (M^+ peak) (Molecular formula: $C_9H_6\ Cl_2N_2S$), 202/204*/206* (58/39.39*/6.06*), 174 (10), 167 (23.8), 132 (11.3), 123 (18.18), 104 (17.0), 87 (11.36), 73 (12.27), 45 (12.27).

Thermal Analysis

Representatively AT-4 is chosen for thermal studies. The TG curve of AT-4 is critically analysed in order to evaluate various kinetic parameters such as n- order of reaction, E- energy of activation, Z- pre-exponential factor, ΔS- entropy change and G- free energy change by using Coats – Redfern (C.R.) (1964), MacCallum-Tanner (M.T.) (1970) and Horowitz-Metzger (H.M.) (1963) method.

Coats-Redfern method

$$\log\frac{1-(1-\alpha)^{1-n}}{(1-n)T^2} = \log\frac{ZR}{Eq} - \frac{E}{2.303R}\times\frac{1}{T} \qquad \text{..... (1)}$$

MacCallum- Tanner Method

$$\log\left(\frac{1-(1-\alpha)^{1-n}}{(1-n)}\right) = \log\frac{ZE}{Rq} - 0.485E^{0.435} - \frac{0.449+0.217E}{T}\cdot 10^3 \qquad \text{.....2}$$

Horowitz – Metzger Method

$$\log\left(\frac{1-(1-\alpha)^{1-n}}{(1-n)}\right) = \log\frac{ZRT_s^2}{Eq} - \frac{E}{2.303\,RT_s} + \frac{E\,\theta}{2.303\,RT_s^2} \qquad \text{.....3}$$

In all three equations: α is fraction decomposed, T_s is temperature at half weight loss, q is rate of heating, θ is difference of particular temperature and temperature at half weight loss ($T-T_s$). The left- hand-side of equation 1 and 2 was plotted against 1/T and against θ ($T-T_s$) for equation 3. By using different values of order of reaction, straight-line was fitted by regression. The highest value of r, the correlation coefficient, gave the correct value of n. From the slope and the intercept, E and Z values were calculated. Using E and Z values, the values of ΔS and G were determined by the equation 4 and 5.

$$\Delta S = 2.303 \times \text{Log}\,[(Z \times h) / (Ts \times k)] \qquad \text{.....4}$$

$$G = E - (\Delta S \times Ts) \qquad \text{.....5}$$

AT-4 undergoes decomposition in two stages, Stage-I: 158^{0}C to 262^{0}C (83.59% weight loss) and Stage-II: 262^{o}C to 600^{o}C (8.25% weight loss). Two DTA peaks (endothermic) are located at 158.74^{0}C and 262.58^{0}C. The residue (5.414%) remaining at the end may be due to formation of thermally stable compound at high temperature. Major weight loss occurs in Stage I only and hence the kinetic parameters (n, E, Z, ΔS and G) have been calculated for this stage. The values of kinetic parameters calculated by Coats – Redfern (C.R.), MacCallum-Tanner (M.T.) and Horowitz-Metzger (H.M.) method are given in Table 2. The values of E (occurring in the range 21-27 Kcal mol^{-1}) and G (22 – 28 Kcal mol^{-1}) are sufficiently high and suggest that DCPAT is a thermally stable compound. The TG-DTA curve is depicted in figure 2.

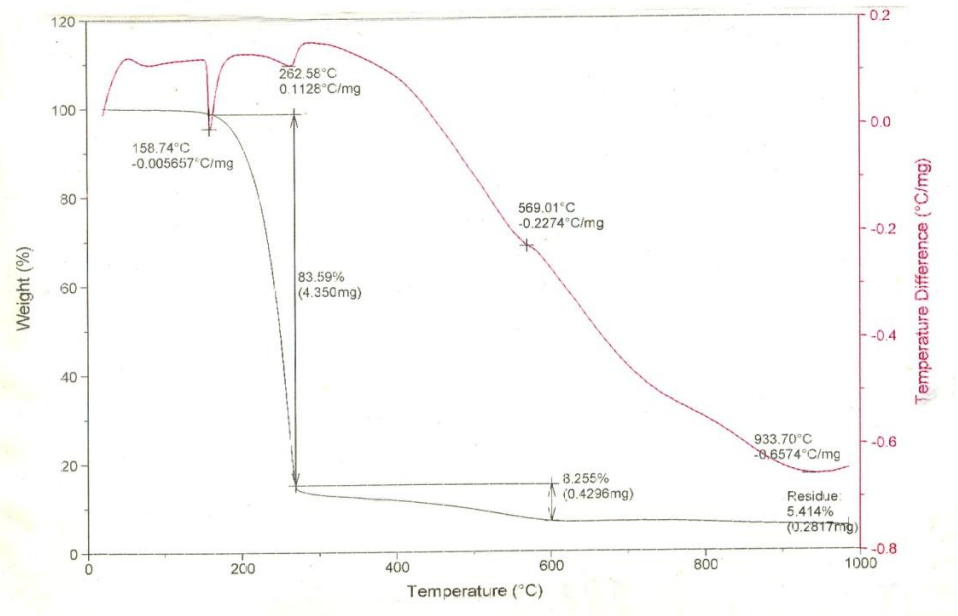

Fig.2: TG-DSC curve of AT-4.

Biological Activity

Substituted 2-aminothiazoles (AT-1 to AT- 4) have been tested for the evaluation of antibacterial activity against *B. subtilis and E. coli* and antifungal activity against *A. niger* and *C. albicans* in ethanol in the concentration range 1-50 µg/ml by serial dilution technique (Spooner, 1972). The MIC values for the Schiff bases (AT-1 to AT- 4) lie in the range **10-20 µg/ml** for antibacterial activity and **08-16 µg/ml** for antifungal activity.

CONCLUSION

MW mediated synthesis of substituted 2-amionothiazole is a convenient and rapid process, as a green approach, resulting in good yield of the expected product. The reaction rate is 200 times faster than the rate of conventional method of synthesis which requires 20 hours heating on water bath. The compounds (AT – 1 to AT –4) are thermally stable. They show good antibacterial and antifungal activity.

ACKNOWLEDGMENTS

Authors are thankful to the authorities of Solapur University, Solapur and D.B.F. Dayanand College of Arts and Science, Solapur, for providing research facilities. Two authors (SVR and RBB) are thankful to UGC – WRO, Pune, for providing grants through minor research project.

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