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A NEW MICROWAVE-ASSISTED METHOD FOR THE SYNTHESIS OF 2-SUBSTITUTED-THIAZOL-4(5H)-ONE VIA HANTZSCH CONDENSATION

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ABSTRACT

A new microwave-assisted method is developed for the synthesis of 2-substituted-thiazol-4(5H)-ones via Hantzsch condensation by a simple experimental protocol without using any catalyst. The products were isolated in excellent yield without any purification. Synthesized compounds were characterized by applying FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral studies and a plausible mechanism is proposed for the formation of the product. The method is versatile for the preparation of a new class of 2-substituted-thiazol-4(5H)-ones.

Keywords: Microwave Heating, 2-substituted-thiazol-4(5H)-one, Hantzsch Condensation, Cyclocondensation.
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INTRODUCTION

Heterocyclic compounds continue to be attractive targets since they exhibit innumerable pharmacological activities.[1–4] Thiazoles are privileged building blocks in medicinal chemistry owing to their diverse pharmacological applications and affinity towards various bio-targets.[5–11] The moiety has grabbed the attention of many organic chemists due to its broad range of pharmacological activities and synthetic diversity. Thiazole derivatives are widely used as antidiabetic,[12–14] antimicrobial,[15–17] anti-inflammatory,[18,19] agents. Specifically, thiazol-4(5H)-one derivatives have shown prominent activity against cancer cell lines.[20,21] These molecules found great applications in medicinal chemistry due to N-C-S bond and carbonyl group in it.[7]

There are many papers published on different synthetic strategies of thiazol-4(5H)-ones using thioglycolic acid,[22–25] ethyl chloroacetate,[26–28] chloroacetic acid.[29] In organic synthesis, microwave heating is an effective method for transforming electromagnetic energy into heat. This technique is unique because of advantages such as rapid reaction rate, higher yields, and simple reaction conditions.[30-31] Prompted by these benefits and our work on the synthesis of biologically active heterocycles,[32-35] we have carried out the reactions under microwave irradiation. In the present study initially, we planned to synthesize 2,4-disubstituted thiazoles by condensing substituted thiosemicarbazones and 2-chloro-*N*-phenethylacetamide via Hantzsch condensation method. Nevertheless, unpredicted products were obtained during our research, which not only helped us to understand our original goal but also inspired us to explore the unexpected mechanism of the reaction.

EXPERIMENTAL

Material and Methods

Shimadzu IR and Bruker AM (400 MHz and 100 MHz) spectrometers were used to study FTIR and NMR (^{1}H and ^{13}C) spectra respectively. Silica gel plate was used to check the progress of the reaction.

Synthesis of 2-(substituted-benzylidene)hydrazinecarbothioamide (3a-3f)

An equimolar mixture of aldehydes **1a-f** (1mmol) and thiosemicarbazide **2** (1mmol) was dissolved in ethanol and refluxed for 1 hour. After the completion of the reaction (checked by TLC, ethylacetate: hexane 2:1) obtained substrate was filtered and dried. Recrystallization of the crude product in ethanol resulted in pale yellow crystals in good yield (90-95%).

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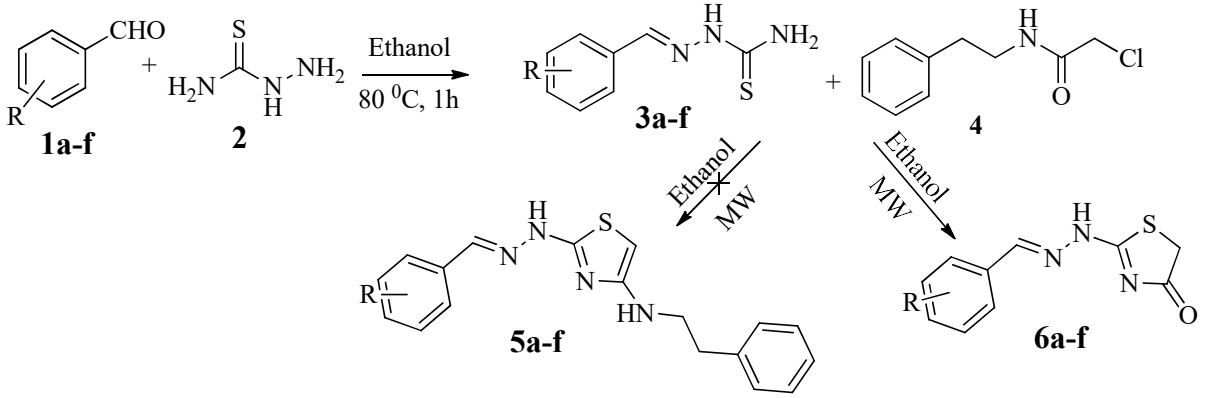


Scheme-1: Synthesis of 2-substituted-thiazol-4(5H)-ones, 6a-f.

Synthesis of 2-(2-(substituted-benzylidene)hydrazinyl)thiazol-4(5H)-one (6a-f) Under Conventional Method

An equimolar mixture of thiosemicarbazone **3a-f** (1.1mmol) and 2-chloro-*N*-phenethylacetamide **4** (1.1mmol) in ethanol (4ml) was heated at 80 ^{0}C for 1.5 hours. The mixture was allowed to cool and the substrate obtained was filtered, recrystallized using DMF:methanol (2:1) to give white crystalline solid **6a-f** in a good yield of 79-90%.

Synthesis of 2-(2-(substituted-benzylidene)hydrazinyl)thiazol-4(5H)-one (6a-f) Under Microwave Heating

An equimolar mixture of thiosemicarbazone **3a-f** (1.1mmol) and 2-chloro-N-phenethylacetamide **4** (1.1mmol) in ethanol (4ml) was heated to 70 ^{0}C at 420W. The reaction was completed within 10-15 minutes and the completion of the reaction was checked by TLC (Toluene:ethyl acetate, 3:1). The reaction product was cooled and the solid obtained was filtered. All synthesized compounds were recrystallized using DMF:methanol (2:1) to give compounds **6a-f** in good yield (82-92 %).

Spectral Data of 2-(2-benzylidenehydrazinyl)thiazol-4(5H)-one (6a)

Melting point = 254-256 °C; FT-IR (cm^{-1}): 1708 (C=N Schiff base), 1639 (C=O of thiazol-4(5H)-one), 1585 (C=N), 755 (CSC); ^{1}H NMR: 3.90 (s, 2H, CH_2), 7.45-7.47 (t, 3H, J = 6.4Hz, ArH), 7.74-7.77 (m, 2H, ArH), 8.40 (s, 1H, CH=N), 11.98 (s, 1H, -NH); ^{13}C NMR: 33.4, 128.0, 129.3, 131.1, 134.5, 156.8, 174.7; MS m/z: 220 (MH^+, 100%), 221, 117, 104.

Spectral Data of 2-(2-(4-methoxybenzylidene)hydrazinyl)thiazol-4(5H)-one (6b)

Melting point = 256-258 °C; FTIR (cm^{-1}): 1718 (C=N Schiff base), 1628 (C=O of thiazol-4(5H)-one), 1561 (C=N), 731 (CSC); ^{1}H NMR: 3.80 (s, 3H, CH_3), 3.88 (s, 2H, CH_2), 7.01 (d, 2H, *J* = 8.8Hz, ArH), 7.69 (d, 2H, *J* = 8.4Hz, ArH), 8.33 (s, 1H, CH=N), 11.91 (s, 1H, -NH); ^{13}C NMR: 33.4, 55.8, 114.8, 127.2, 129.7, 156.3, 161.7, 174.5; MS m/z: 250 (MH^+, 100%).

Spectral Data of (E)-2-(2-(4-methylbenzylidene)hydrazinyl)thiazol-5(4H)-one (6c)

Melting point = 268-270 °C; FTIR (cm^{-1}): 1710 (C=N Schiff base), 1630 (C=O of thiazol-4(H)-one), 1570 (C=N), 740 (CSC); ^{1}H NMR: 2.34 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 7.28 (d, 2H, *J* = 7.6Hz, ArH), 7.66 (d, 2H, *J*= 8.0Hz, ArH), 8.36 (s, 1H, CH=N), 11.95 (s, 1H, -NH); ^{13}C NMR: δ 21.5, 33.4, 128.1, 129.9, 131.9, 141.0, 156.6, 165.1, 174.6; MS m/z: 234 (MH^+, 100%).

Spectral Data of (E)-2-(2-(3,4-dichlorobenzylidene)hydrazinyl)thiazol-5(4H)-one (6d)

Melting point = 306-308 °C; FTIR (cm^{-1}): 1712 (C=N Schiff base), 1635 (C=O of thiazol-4(H)-one), 1580 (C=N), 750 (CSC), 730 (C-Cl); ^{1}H NMR: 3.91 (s, 2H, CH_2), 7.75 (s, 2H, ArH), 7.96 (s, 1H, ArH), 8.14 (s, 1H, CH=N), 12.05 (s, 1H, -NH); ^{13}C NMR: δ 33.5, 127.6, 129.7, 131.6, 132.1, 133.3, 135.4, 154.4, 174.0; MS m/z: 287 (MH^+, 100%).

Spectral Data of (E)-2-(2-(4-chlorobenzylidene)hydrazinyl)thiazol-5(4H)-one (6e)
Melting point = 300-302 ℃; FTIR (cm^{-1}): 1709 (C=N Schiff base), 1632 (C=O of thiazol-4(H)-one), 1575 (C=N), 754 (CSC), 700 (C-Cl); ^{1}H NMR: 3.90 (s, 2H, CH_2), 7.55 (d, 2H, *J* = 8.4Hz, ArH), 7.78 (d, 2H, *J* = 8.4Hz, ArH), 8.41 (s, 1H, CH=N), 12.00 (s, 1H, -NH); ^{13}C NMR: 33.5, 129.4, 129.7, 133.5, 135.5, 155.5, 166.1, 174.5; MS m/z: 254 (MH^+, 100%).

Spectral Data of (E)-2-(2-(4-fluorobenzylidene)hydrazinyl)thiazol-5(4H)-one (6f)
Melting point = 280-282 ℃; FTIR (cm^{-1}): 1715 (C=N Schiff base), 1637 (C=O of thiazol-4(H)-one, 1581 (C=N), 1100 (C-F), 755 (CSC); ^{1}H NMR: 3.90 (s, 2H, CH_2), 7.29-7.33 (t, 2H, *J* = 9.2Hz, ArH), 7.80-7.83 (m, 2H, ArH), 8.41 (s, 1H, CH=N), 11.98 (s, 1H, -NH); ^{13}C NMR: δ 33.5, 126.8, 128.7, 130.6, 131.8, 152.6, 164.3, 173.9; MS m/z: 238 (MH^+, 100%).

RESULTS AND DISCUSSION

An equimolar mixture of substituted benzaldehydes **1a-f** and thiosemicarbazide **2** was refluxed in ethanol for 1h. The halt of the reaction was confirmed through TLC and the product was cooled and the thiosemicarbazones **3a-f** formed were filtered. Thiosemicarbazones **3a-f** were condensed with 2-chloro-*N*-phenethylacetamide **4** in ethanol to give 2-substituted-thiazol-4(5H)-ones **6a-f**. Similarly, the reaction was carried out under microwave using the same reaction condition. In comparison to the conventional method, the microwave method resulted in good yields (82-92%) in less time. In the conventional method, the reaction was completed in 1.5 hours, while under MWI the reaction was completed in 10-15 minutes. The comparative study of conventional and microwave methods is shown in Table-1. Characterization of all the molecules was performed using FTIR, ^{1}H NMR, ^{13}C NMR, and MS studies.

In FT-IR spectra, the peaks in the range 1708-1718 cm^{-1} and 1628-1639 cm^{-1} indicate the presence of imine group of schiff base and carbonyl group of thiazol-4(5H)-one respectively. Also, bands in the range from 1561-1585 cm^{-1} and 731-755 cm^{-1} shows the existence of C=N and C-S-C bond respectively. ^{1}H NMR spectra showed a singlet in the range δ 3.88-3.90 ppm resulting from methylene protons of thiazol-4(5H)-one. The aromatic protons are observed in the range form δ 7.01 to 7.77 ppm. The highly deshielded singlets in the region δ 8.33-8.40 ppm and 11.91-11.98 ppm indicate the presence of CH=N proton and –NH proton respectively. The proton NMR of **6b** indicated a highly shielded singlet peak at δ 3.80 ppm due to the presence methyl group. The absence of a peak at 11.98 ppm in D_2O exchange is affirmative of –NH group in the molecule. In ^{13}C NMR spectra, shielded peak at 33.46 ppm indicating the thiazol-4(5H)-one methylene carbon. The peaks at δ 128-134 ppm correspond to the aromatic carbons. The imine carbon (CH=N) and carbonyl carbon were present in the range from δ 154.4-166.1 ppm and 173.9-174.7 ppm respectively. The ^{13}C NMR spectrum of **6b** showed a shielded peak at δ 55.8 ppm indicating the presence of methyl carbon. The mass spectrometry gave protonated molecular ion peak (MH^+) at m/z 220, which confirms the formation of compound **6a**. Peaks at m/z 116.9 and 104.0 correspond to the fragments **6a1** and **6a2** respectively (Fig.-1).

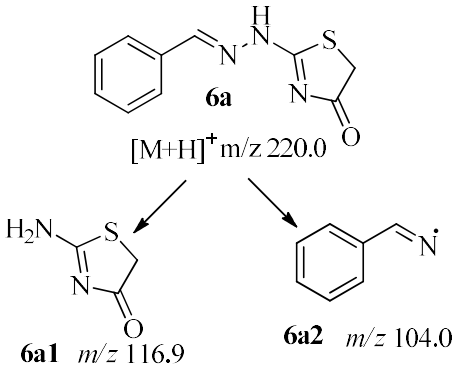


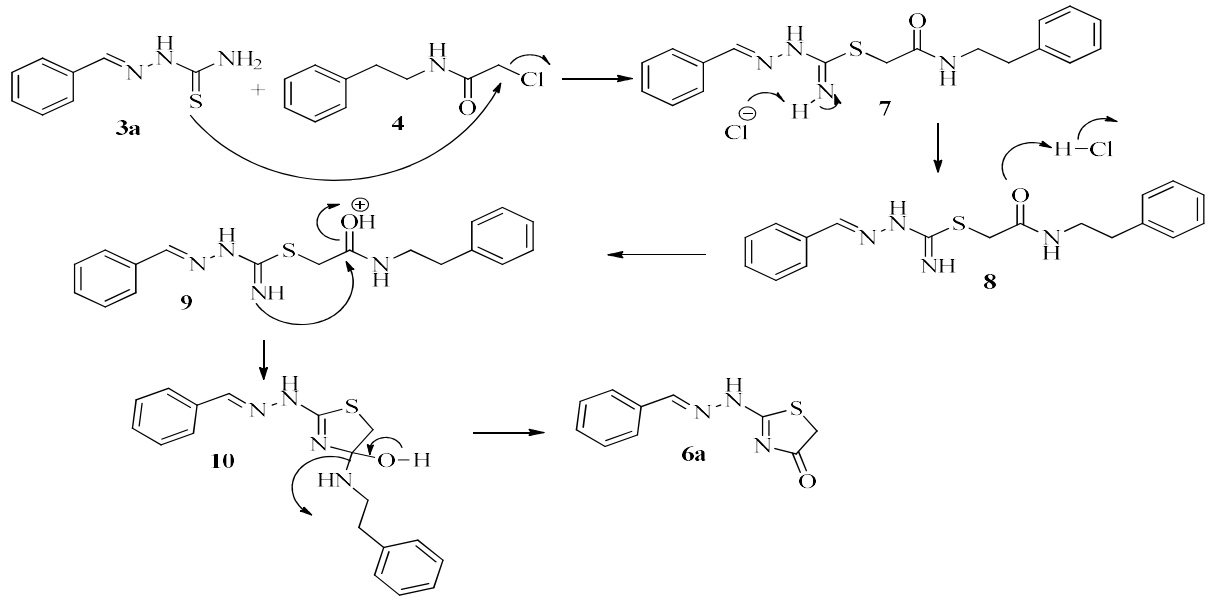
Fig.-1: Mass Fragmentation Study of Compound 6a

A plausible mechanism of the reaction for the formation 2-(2-benzylidenehydrazinyl)thiazol-4(5H)-one **6a** was proposed (Scheme-2). The first step involves the nucleophilic attack of thiol **3a** on methylene group (CH_2-Cl) of **4**, followed by the elimination of HCl. This attack results in the formation of a new C-S bond

7. Protonation of intermediate **7** by the released HCl gives intermediate **8**, which eventually undergoes cyclization by the attack of imine nitrogen on electron-deficient protonated carbonyl group to give hydroxy compound **9**. In the next step, we expected compound **5a** with the elimination of the water molecule. However, 2-substituted-thiazol-4(5H)-one **6a** was obtained by proton shift with the elimination of phenylethylamine.

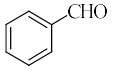
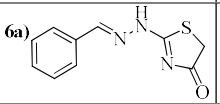
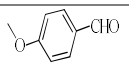
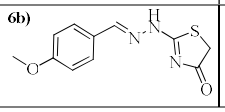
Further, the reaction conditions were optimized by carrying the reaction in different solvents and temperatures and the results are shown in Table-2. The reaction was first carried out at room temperature and then at 50 ^{0}C, but in both conditions, the product was not formed. Then the temperature was raised to 60 ^{0}C and stirred for one hour. The product was precipitated in all the solvents and it was filtered. Table-1 shows the yields and melting points of the compounds.

In ethanol, the pale yellow colored product was obtained, which was recrystallized in DMF: water (2:1). After the recrystallization, white-colored crystals were obtained in 83% of yield. Similarly, in water and DMF, 70% and 72% of the product were obtained respectively, after recrystallization. In the case of methanol and acetonitrile, after the reaction white colored crystals were obtained without recrystallization. A lower yield of **6a** (50%) was observed when methanol was used as a solvent. Due to the polar nature of the methanol, the formed product got dissolved in methanol and hence lower yield was observed. In acetonitrile 86% yield was observed without recrystallization, after 1.5 hours stirring at 60 ^{0}C. From Table-2 we can conclude that, among the tested solvents, the quality of the product and yield was good when acetonitrile was used as a solvent.



Scheme-2: A Plausible Mechanism for the unexpected 2-substituted –thiazol-4(5H)-one, 6a

Table-1: Synthesis of 2-substituted-thiazol-4(5H)-one 6a-f using substituted thiosemicarbazones and 2-chloro-N-phenethylacetamide in ethanol.

Entry	Aldehydes	Products	Melting Point (°C)	Conventional Method		Microwave Method	
				Time (hours)	Yield (%)	Time (min)	Yield (%)
1			254-256	1.5	83	10	88
2			256-258	1.5	79	10	82

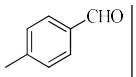
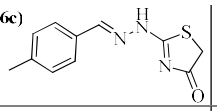
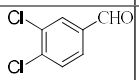
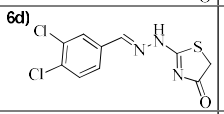
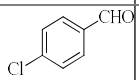
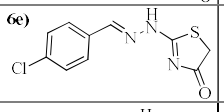
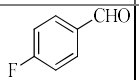
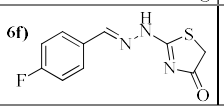
3			268-270	1.5	80	15	84
4			306-308	1.5	90	15	92
5			300-302	1.5	83	10	87
6			280-282	1.5	84	10	86

Table-2: Effect of Solvents on the Synthesis of 6a, at 60 ºC

Entry	Solvents	Yield (%)
1	Ethanol	83[a]
2	Water	70[a]
3	Dimethylformamide	72[a]
4	Acetonitrile	86
5	Methanol	50

[a] = Yield after recrystallization in DMF:water (2:1)

CONCLUSION

In conclusion, we report a new method for making 2-substituted-thiazol-4(5H)-ones **6a-f** via Hantzsch condensation without using any catalyst. Comparative studies with conventional methods indicate the microwave heating method resulted in better yield in less time. The method is simple, versatile, and resulted in excellent yield in the range of 82-92%.

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