A facile synthesis of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one using microwave irradiation and conventional method

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A facile synthesis of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one using microwave irradiation and conventional method

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Abstract

A new effective approach to the synthesis of some new (*Z*)-5-(substituted)-2-thioxothiazolidin-4-one **3a-l** and (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one **5a-l** is reported under microwave irradiation as well as conventional conditions.

Keywords: aromatic aldehydes, 2-thioxothiazolidin-4-one, microwave irradiation,

In recent years, thiazolidinone and their derivatives have become among the most extensively investigated compounds. They constitute a very important group of heterocyclic compounds, having valuable biological activities in the areas of medicine as well as agriculture. The rhodanine scaffold is a central part of biologically active compounds with various applications and uses[1,2] such as antimicrobial,[3,4] antimalarial,[5] anti-HIV agents,[6-9] anti-inflammatory,[10,11] antifungal,[12,13] anticancer,[14] antidiabetic[15] and anti-tubercular.[16,17] For the discovery of new lead structures in drug discovery, based on high throughput screening, synthetic methodologies are required which deliver highly diverse derivatives in a timely manner. Under these circumstances, microwave-assisted chemistry appears to be a promising synthetic method.[18] Utility of microwave irradiation[19] (MW) to carry out organic reaction has now become a regular feature. The main benefits of performing the reaction under microwave conditions are the significant rate-enhancements and the higher product yields and minimum time requirement. Here, we wish to mention the development and implementation of a methodology allowing for the synthesis of some new (*Z*)-5-(substituted)-2-thioxothiazolidin-4-one **3a-l** and (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one **5a-l** derivatives. The reported reactions under microwave irradiation as well as by conventional method proceed in short

reaction times and give good to excellent yields. The structures of compounds **3a-l** and **5a-l** were substantiated by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis and only the thermodynamically more stable *Z*-isomers were obtained.[20]

We have developed the protocol for the synthesis of (*Z*)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one **3** (Scheme 1) by condensation between active methylene compounds and aromatic aldehydes. The reaction of 2-chlorobenzaldehyde (1 mmol) and 2-thioxothiazolidin-4-one (rhodanine) (1 mmol) catalyzed by various bases and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvent on the condensation reaction, acetic acid was found to be the best solvent for the reaction (Table 1, entry 8); other solvents, including dichloromethane (DMF), ethanol, methanol and toluene were less efficient (Table 1, entries 1, 2, 4-7, 9-10, 14, 15). Ethanol gave the corresponding product in a 50-55% yield, which was the worst among these solvents (Table 1, entry 1, 6, 11). Nevertheless, all of these yields were generally low before further optimizations. To increase the efficiency of the condensation reaction, the effects of different bases were investigated (Table 1, entries 1-15). Sodium acetate exhibited the best performance with acetic acid solvent (55-90%). Ammonium acetate and piperidine gave lower yields with other solvents, but gave better yield in combination with acetic acid as a solvent (Table 1, entries 3 and 13). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 1 mL of acetic acid turned out to be the best choice with yields of 75%, 90% and 80% (Table 1, entry 3, 8 and 13). We would like to mention here that acetic acid as a solvent with sodium acetate as base was the best choice with a yield of 90% and less time required for the completion of the reaction (Table 1, entry 8). Thus we decided to carry out the reactions in acetic acid with sodium acetate.

The compounds **2a-l** were then subjected to a Knoevenagel condensation with the appropriate rhodanines, which were synthesized using the reported procedure,[21,22] to provide new series of target compounds **3a-l**. Thiazolidinone based compounds were synthesized by microwave irradiation (MW) as well as conventional heating with sodium acetate and glacial acetic acid.[23]

We synthesized the new (*Z*)-5-(substituted)-2-thioxothiazolidin-4-one **3a-l** (Scheme 2, Table 2) derivatives and (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one **5a-l** (Scheme 3,

Table 3) derivatives under microwave irradiation as well as conventional method. However, the MW reaction provided cleaner reaction, short reaction time, and the products were only required to be washed with ice-cold water. The yields were good to excellent. The IR spectrum of representative compound (Z)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one **3a**, shows a strong absorption band at 1694 cm^{-1} which is due to a carbonyl group thiazolidinone moiety. The mass spectrum revealed a molecular ion peak at m/z = 256 (M+H) corresponding to a molecular formula $C_{10}H_6ClNOS_2$. ^1H NMR spectra of compounds **3a** show only one signal for the methyne proton in the range δ 7.79–7.91 ppm, at lower field values than those expected for the *E*-isomers. This strongly indicates that the compounds have the *Z*-configuration. The compounds **5a-l** were synthesized from compound **3a-l** and IR spectrum of representative compound (Z)-5-(2-chlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one **5a**, showed a strong absorption band at 1697 cm^{-1} due to a carbonyl group. The mass spectrum revealed a molecular ion peak at m/z = 270 (M+H) corresponding to a molecular formula $C_{11}H_8ClNOS_2$.

In conclusion, we have successfully developed an easy access to a new series of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one **5a-l** derivatives. The mild reaction conditions, good to excellent yields, easy workup, and easily available substrates make the reactions attractive for the preparation of compounds **3a-l** and **5a-l**. Efforts towards the synthesis of other important drug molecules with a Rhodanine moiety by MW irradiation as well as conventional method are ongoing in our laboratory. Also work is in progress to obtain biological activity such as antibacterial, antifungal and anticancer of these important compounds. Results in these areas will be presented in due course.

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23. (a) General procedure for the synthesis of compounds (**3a-l**)

Method A: Microwave-assisted synthesis:

In a 100 ml round bottom flask, equimolar amounts of 2-thioxothiazolidin-4-one **1** (1 mmol), anhydrous sodium acetate (1 mmol) were added in glacial acetic acid (1 mL) and then aromatic aldehydes **2a-l** (1 mmol) were added to the reaction mixture. This mixture was subjected to MW irradiation (800 W), at 110 ºC temperature for 14-18 min. The progress of reaction was monitored by TLC (20% ethyl acetate: *n*-hexane). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered off and washed with water (3×15 mL), dried, and purified by recrystallization in ethanol as solvent to give 92-98% yield.

Method B: Conventional synthesis:

In a 100 ml round bottom flask, equimolar amounts of 2-thioxothiazolidin-4-one **1** (1 mmol), anhydrous sodium acetate (1 mmol) were added in glacial acetic acid (1 mL) and then aromatic aldehydes **2a-l** (1 mmol) were added to the reaction mixture. The

mixture was stirred under reflux condition for 4-8 h. The progress of reaction was monitored by TLC (20% ethyl acetate: *n*-hexane). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered off and washed with water (3×15 mL), dried, and purified by recrystallization in ethanol as solvent to give 85-90 % yield.

*(Z)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one (**3a**)*

Yellow solid. Yield: 98%. mp 180–182 ºC; ES-MS m/z (%): 256 (M+H). IR νmax/cm^{-1}: 3033 (NH), 2829 (CH–Ar), 1694 (C=O), 1581 (C=C), 1465 (C=N), 1189 (C=S), 1038 (C–N). ^{1}H NMR (400 MHz, DMSO-d6): δppm = 7.23–7.48 (m, 4H, Ar–CH), 7.79–7.91 (s, 1H, =CH), 13.71–13.92 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6): δppm = 116.6, 126.5, 127.5, 129.4, 129.9, 133.4, 143.5, 168.7, 193.5. Molecular formula $C_{10}H_6ClNOS_2$

*(Z)-5-(2,4-dichlorobenzylidene)-2-thioxothiazolidin-4-one (**3b**)*

Yellow solid. Yield: 98%. mp 230–232 ºC; ES-MS m/z (%): 291 (M+H). IR νmax/cm^{-1}: 3039 (NH), 2929 (CH–Ar), 1728 (C=O), 1574 (C=C), 1442 (C=N), 1193 (C=S), 1047 (C–N). ^{1}H NMR (400 MHz, DMSO-d6): δppm = 7.33–7.61 (m, 3H, Ar–CH), 7.77–7.90 (s, 1H, =CH), 13.81–13.99 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6): δppm = 116.2, 125.2, 126.5, 128.4, 130.9, 131.4, 136.5, 143.2, 168.3, 193.3. Molecular formula $C_{10}H_5Cl_2NOS_2$

*(Z)-5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one (**3c**)*

Yellow solid. Yield: 95%. mp 247–249 ºC; ES-MS m/z (%): 252 (M+H). IR νmax/cm^{-1}: 3049 (NH), 2932 (CH–Ar), 1729 (C=O), 1575 (C=C), 1447 (C=N), 1198 (C=S), 1049 (C–N). ^{1}H NMR (400 MHz, DMSO-d6): δppm = 3.71–3.83 (s, 3H, OCH_3). 6.90–7.01 (d, 2H, Ar–CH), 7.40–7.51 (d, 2H, Ar–CH), 7.79–7.90 (s, 1H, =CH), 13.71–13.93 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6): δppm = 55.8, 114.2, 116.3, 127.4, 130.2, 143.5, 159.3, 168.4, 193.5. Molecular formula $C_{11}H_9NO_2S_2$

(b) General procedure for the synthesis of compounds (**5a-l**)

Method A: Microwave-assisted synthesis**:**

In a 100 ml round bottom flask, the compound **3a-l** (1 mmol) and triethylamine (1.2 mmol) dissolved dichloromethane (1 mL) with iodomethane (1.2 mmol) were taken

and this mixture subjected to MW irradiation (800 W), at 40 ºC temperature for 2-5 min. The progress of reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction, the reaction mixture was concentrated *in vacuo*. The residue was washed with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 88-92%.

Method B: Conventional synthesis:

In a 100 ml round bottom flask, the compound **3a-l** (1 mmol) and triethylamine (1.2 mmol) were added to dichloromethane (1 mL) at room temperature. To the stirred reaction mixture, iodomethane (1.2 mmol) was added and stirred for 1-2 h at room temperature. The progress of the reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction the reaction mixture was concentrated *in vacuo*. The residue was washed with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 60-77%.

*(Z)-5-(2-chlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (**5a**)*

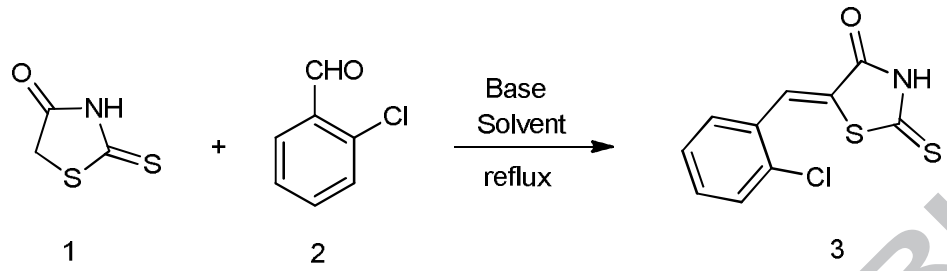
Yellow solid. Yield: 92%. mp 170–172 ºC; ES-MS m/z (%): 271 (M+H). IR νmax/cm^{-1}: 3021 (CH–Ar), 1697 (C=O), 1603 (C=C), 1504 (C=N), 1154 (C-S), 982 (C–N). ^{1}H NMR (400 MHz, DMSO-d6): δppm = 2.71–2.87 (s, 3H, S–CH_3), 7.41–7.71 (m, 4H, Ar–CH), 7.82–7.95 (s, 1H, =CH). ^{13}C NMR (100 MHz, DMSO-d6): δppm = 14.2, 126.5, 127.6, 129.4, 129.9, 132.2, 133.1, 134.2, 152.2, 162.8, 167.2. Molecular formula $C_{11}H_8ClNOS_2$.

*(Z)-5-(2,4-dichlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (**5b**)*

Yellow solid. Yield: 90%. mp 165–167 ºC; ES-MS m/z (%): 305 (M+H). IR νmax/cm^{-1}: 3009 (CH–Ar), 1705 (C=O), 1579 (C=C), 1478 (C=N), 1137 (C-S), 980 (C–N). ^{1}H NMR (400 MHz, DMSO-d6): δppm = 2.71–2.87 (s, 3H, S–CH_3), 7.31–7.61 (m, 3H, Ar–CH), 8.02–8.13 (s, 1H, =CH). ^{13}C NMR (100 MHz, DMSO-d6): δppm = 14.3, 125.3, 126.5, 128.8, 130.2, 131.2, 132.2, 136.2, 152.1, 162.7, 167.1. Molecular formula $C_{11}H_7Cl_2NOS_2$.

Scheme 1

Screening of model reaction (*Z*)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one (**3**)[a]

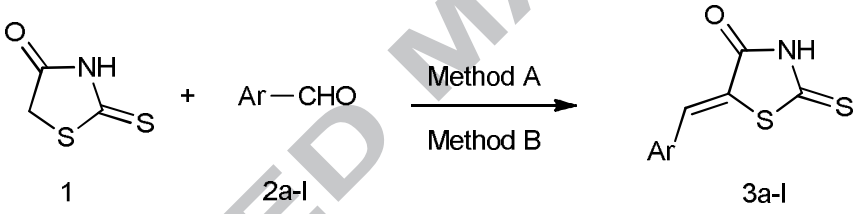


1 2 3

[a]Reaction condition (**3a**). 2-thioxothiazolidin-4-one (**1**) (1 mmol), 2-chlorobenzaldehyde (**2**) (1 mmol), Base (1 mmol), solvent 1mL, reflux 6-13 h.

Scheme 2

Synthesis of (*Z*)-5-(substituted)-2-thioxothiazolidin-4-one (**3a-l**)[a]



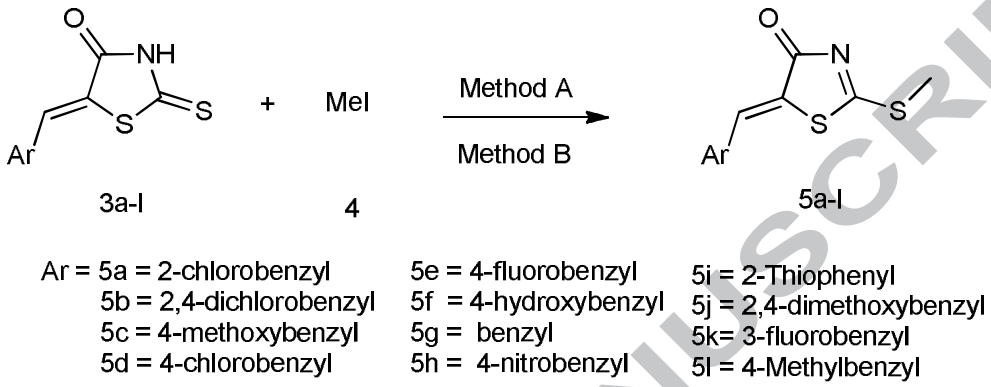
1 2a-l 3a-l

Ar = 3a = 2-chlorobenzyl
3b = 2,4-dichlorobenzyl
3c = 4-methoxybenzyl
3d = 4-chlorobenzyl
3e = 4-fluorobenzyl
3f = 4-hydroxybenzyl
3g = benzyl
3h = 4-nitrobenzyl
3i = 2-Thiophenyl
3j = 2,4-dimethoxybenzyl
3k= 3-fluorobenzyl
3l = 4-Methylbenzyl

[a]Reaction condition (**3a-l**). **1** (1mmol), **2a-l** (1mmol), sodium acetate (1mmol), 1 mL acetic acid, **Method A:** Microwave-assisted synthesis: 110 ºC, 14-18 min. **Method B:** Conventional synthesis: reflux 4-8 h.

Scheme 3

Synthesis of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one (**5a-l**)[a]



Ar = 5a = 2-chlorobenzyl
5b = 2,4-dichlorobenzyl
5c = 4-methoxybenzyl
5d = 4-chlorobenzyl
5e = 4-fluorobenzyl
5f = 4-hydroxybenzyl
5g = benzyl
5h = 4-nitrobenzyl
5i = 2-Thiophenyl
5j = 2,4-dimethoxybenzyl
5k= 3-fluorobenzyl
5l = 4-Methylbenzyl

[a]Reaction condition (**5a-l**). Compounds **3a-l** (1 mmol), **4** (1.2 mmol), **Method A:** Microwave-assisted synthesis: 40ºC, triethylamine (1.2 mmol), 1 mL dichloromethane, 2-5 min. **Method B:** Conventional synthesis: triethylamine (1.2 mmol), 1 mL dichloromethane, stirring room temperature, 1-2 h.

Table 1 Screening of catalyst, solvents, reaction time, and yield for the synthesis (**3**)[a]

Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	Ammonium acetate	Ethanol	10	50
2	Ammonium acetate	DMF	12	55
3	Ammonium acetate	Acetic acid	11	75
4	Ammonium acetate	Methanol	10	60
5	Ammonium acetate	Toluene	11	50
6	Sodium acetate	Ethanol	11	55
7	Sodium acetate	DMF	10	58
8	Sodium acetate	Acetic acid	6	90
9	Sodium acetate	Methanol	12	65
10	Sodium acetate	Toluene	10	60
11	Piperidine	Ethanol	12	55
12	Piperidine	DMF	11	58
13	Piperidine	Acetic acid	12	80
14	Piperidine	Methanol	12	60
15	Piperidine	Toluene	13	52

[a] All the reaction was carried out in equimolar amounts of each compound in 1 mL of solvent .

[b] Isolated yield.

Table 2 Synthesis of (Z)-5-(substituted)-2-thioxothiazolidin-4-one (**3a-l**)[a]

Entry	Ar	Product	Time		Yield[b] (%)		M.P. (°C)
			MW (min)	Conventional (h)	MW	Conventional	
1	2-chlorobenzyl	**3a**	18	6	98	90	180-182
2	2,4-dichlorobenzyl	**3b**	18	6	98	90	230-232
3	4-methoxybenzyl	**3c**	15	6	95	88	247-249
4	4-chlorobenzyl	**3d**	15	7	95	86	131-133
5	4-fluorobenzyl	**3e**	14	7	94	85	226-228
6	4-hydroxybenzyl	**3f**	18	6	95	85	265-267
7	benzyl	**3g**	14	5	95	85	204-206
8	4-nitrobenzyl	**3h**	14	4	95	90	255-257
9	2-Thiophenyl	**3i**	18	8	92	85	231-233
10	2,4-dimethoxybenzyl	**3j**	15	8	94	85	271-273
11	3-fluorobenzyl	**3k**	16	7	95	85	198-200
12	4-Methylbenzyl	**3l**	18	8	92	85	219-221

[a]Reaction condition (**3a-l**).

Method A: Microwave-assisted synthesis: Acetic acid, Sodium acetate, 110 °C, 14-18 min.

Method B: Conventional synthesis: Acetic acid, Sodium acetate, reflux 4-8 h.

[b]Isolated yields.

Table 3 Synthesis of (Z)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one (**5a-l**)[a].

Entry	Ar	Product	Time		Yield[b] (%)		M.P. (ºC)
			MW (min)	Conventional (h)	MW	Conventional	
1	2-chlorobenzyl	**5a**	2	1	92	75	170-172
2	2,4-dichlorobenzyl	**5b**	4	1	90	72	165-167
3	4-methoxybenzyl	**5c**	2	1	90	65	162-164
4	4-chlorobenzyl	**5d**	2	1	92	65	160-162
5	4-fluorobenzyl	**5e**	3	1	90	75	143-145
6	4-hydroxybenzyl	**5f**	3	2	90	65	222-224
7	benzyl	**5g**	5	2	88	75	145-147
8	4-nitrobenzyl	**5h**	5	1	92	65	160-162
9	2-Thiophenyl	**5i**	3	2	92	67	150-152
10	2,4-dimethoxybenzyl	**5j**	4	2	90	77	172-174
11	3-fluorobenzyl	**5k**	5	1	90	72	160-162
12	4-Methylbenzyl	**5l**	4	1	90	60	175-177

[a]Reaction condition (**5a-l**).

Method A: Microwave-assisted synthesis: Triethylamine, Dichloromethane , 40 ºC, 2-5 min.

Method B: Conventional synthesis: Triethylamine, Dichloromethane, room temperature, 1-2 h.

[b]Isolated yields.

Research highlights:

- Synthesis of important drug molecules with a Rhodanine moiety by MW irradiation as well as conventional method.
- We have successfully developed an easy access to a new series of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one.
- Developed the mild reaction conditions, well to excellent yields, easy workup.

A facile synthesis of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one using microwave irradiation and conventional method

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Graphical Abstract