European Journal of Chemistry

Journal webpage: www.eurjchem.com

# Alum [$KAl(SO_4)_2 \cdot 12H_2O$] catalyzed microwave assisted synthesis of 5-arylidine-2-(methylthio)-thiazolone derivatives in water

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ARTICLE INFORMATION

DOI: 10.5155/eurjchem.6.4.410-416.1312

Received: 22 August 2015
Received in revised form: 14 September 2015
Accepted: 19 September 2015
Published online: 31 December 2015
Printed: 31 December 2015

KEYWORDS

Alum
Water
Aldehyde
Rhodanine
Triethyl amine
Microwave-assisted synthesis

ABSTRACT

An efficient and environmentally benign method has been developed for the synthesis of 5-arylidine-2-(methylthio)-thiazolones derivatives using Alum [$KAl(SO_4)_2 \cdot 12H_2O$] catalyst and triethyl amine in water under microwave irradiation. This green transformation generated one C-S and one C-C bond, condensation and S-methylation. Notable advantages for the present protocol include, short reaction time, cleaner reaction profile and easy isolation of product by microwave irradiation technique using green catalyst and solvent.

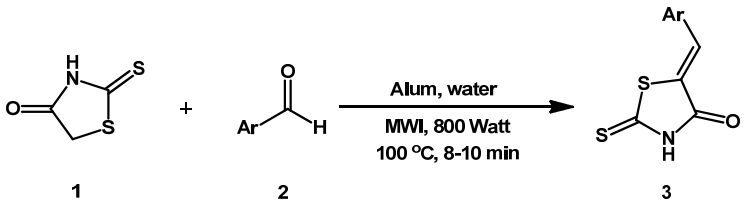
**Cite this**: *Eur. J. Chem.* **2015**, *6(4)*, 410-416

## 1. Introduction

In recent years, development of atom economical and environmentally benign chemical technologies has become an important goal in the synthetic chemistry; [1-3] in improvation, organic chemist have developed an eco-friendly methods such as use of microwave, ultrasound, grinding, ball mill reaction and so on. The use of microwave energy is one of the eco-friendly methods to accelerate the organic reactions which attract attention of many researchers and have number of advantages such as short reaction time, easy work-up procedure, no side product and high yield. Hence, among various green methodologies, Microwave irradiation method mostly used and found promising in organic synthesis [4-6]. Alum ($KAl(SO_4)_2 \cdot 12H_2O$), which is used for prominent organic transformations, for example the Beginelli reaction [7] synthesis of coumarins, [8] and also used for the synthesis of 1,8-dioxo-octahydroxanthenes [9], isoquinolonic acids [10], trisubstituted dimidazoles [11], 1*H*-spiro[isoindoline-1,2'-quinazoline]-3,4'(3*H*)-diones [12], 1,3,4-oxadiazoles [13], and 1,5-benzodiazepines [14]. Use of water as a reaction medium results in increase the rate and selectivity of many organic reactions [15-19]. In addition to using of green solvent with or without combination of microwave irradiation reactions were performed and found reduced reaction time compared to conventional method [20-28].

The rhodanine scaffold is central part of biologically active, pharmaceutically important compounds with various application and uses such as anti-microbial [29-32], anti-diabetic [33,34], anti-malarial [35], anti-fungal [36], anti-inflammatory [37], anti-tubercular [38,39], anti-HIV [40,41], inhibitors of chikungunya virus [42-44], anti-cancer and anti-leukotriene therapy [45,46]. Previously reported synthetic methods [47-56]; these synthetic approaches, however, suffer from disadvantages such as using hazardous solvent and or catalyst, low yield, lack of selectivity, and complicated workup in procedures, use of hazardous chemical compounds and are expensive. To convey these difficulties, it is essential to develop a simple and eco-friendly method for the synthesis of (*Z*)-5-substituted(aryl/hetero-aryl)-2-(methylthio)-thiazolones.


ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online) 
http://dx.doi.org/10.5155/eurjchem.6.4.410-416.1312




**Scheme 1**

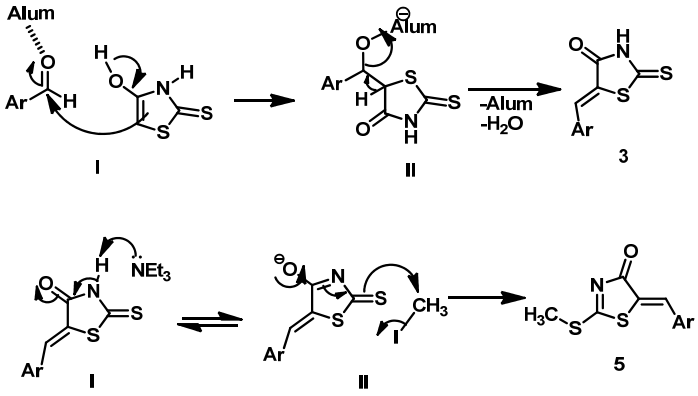



**Figure 1.** Plausible mechanism for the synthesis of functionalized thiazolidinones.

Present study is outcome of our continuous efforts which establish new green combination of triethyl amine and water as catalyst and solvent. They have become an increasingly attractive synthetic tool because of their green credentials such as convergence, atom-economy, energy and cost savings, with minimal waste [57]. Present study is in continuation of our research interest as searching of new and facile green synthetic protocols [58-63].

## 2. Experimental

### *2.1. Instrumentation*

Melting points were recorded on SRS Optimelt melting point apparatus and are uncorrected. The IR spectra were run for KBr discs on a FT-IR Bruker ($\nu_{max}$ in $cm^{-1}$) and $^1H$ NMR and $^{13}C$ NMR, were recorded on a 400 MHz, NMR instrument Bruker (Avance) DMSO-$d_6$ as solvent. Mass spectra were taken with Micromass-QUATTRO-II mass spectrometer. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz. Silica gel-G plates (Merck) were used for thin layer chromatography analysis with a mixture of (10% chloroform:methyl alcohol) as eluent. Elemental analysis was performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Microwave reactions have been carried out in a MicroSYNTH Lab station of Ethusi Milestone.

### *2.2. Synthesis*

#### *2.2.1. General method for synthesis of (Z)-5-(benzylidine)-2-thioxothiazolidin-4-one (3)*

In a small round bottom flask, rhodanine **1** (1 mmol), aldehyde **2** (1 mmol), alum 10 mol% in minimum amount of water were added, reaction mixture was subjected to microwave irradiation (800 Watt at 100 °C) for 8-10 min. The progress of reaction was monitored by thin layer chromatography(ethyl acetate:*n*-hexane; 3:7, *v*:*v*) after completion of reaction, the reaction mixture poured into ice-cold water, precipitate was filtered and wash with water dried, purified by recrystallization in ethyl alcohol as solvent, yield 89-98% (Scheme 1 and Figure 1).

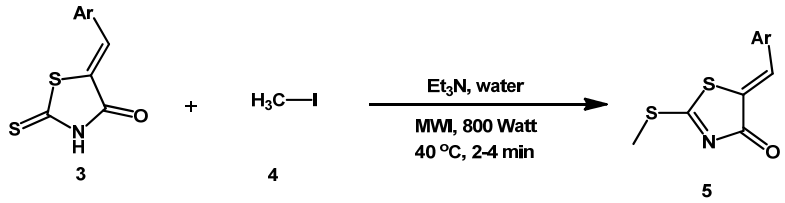
*(Z)-5-Benzylidene-2-thioxothiazolidin-4-one* (**3a**): Color: Yellow crystal. Yield: 90%. M.p.: 203-205 °C. FT-IR (KBr, ν, $cm^1$): 1236 (N-C=S), 1690 (N-C=O), 1585(N-H), 2050 (Ar-H), 1735. $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.50-7.64 (m, 5H, Ar-H), 7.65 (s, 1H, =CH), 13.85 (s, 1H, N-H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 135.7, 129.02, 128.7, 128.4, 128.2, 127.03, 116.2. MS (ESI, *m/z*): 222 $[M+H]^+$.

*(Z)-5-(4-Chlorobenzylidene)-2-thioxothiazolidin-4-one* (**3b**): Color: Yellow crystal. Yield: 91%. M.p.: 130-132 °C. FT-IR (KBr, ν, $cm^1$): 1230 (N-C=S), 1695 (N-C=O), 1589 (N-H), 3025 (Ar-H), 1120 (C-F). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.38-7.70 (d, 4H, Ar-H), 7.72 (s, 1H, =CH), 13.93 (s, 1H, N-H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 133.7, 129.02, 128.7, 128.4, 128.2, 127.03, 116.5. MS (ESI, *m/z*): 255 $[M+H]^+$.

*(Z)-5-(4-Fluorobenzylidene)-2-thioxothiazolidin-4-one* (**3c**): Color: Yellow crystal. Yield: 90%. M.p.: 225-227 °C. FT-IR (KBr, ν, $cm^1$): 1230 (N-C=S), 1694 (N-C=O), 1580 (N-H), 3025 (Ar-H), 1125 (C-F). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.65 (d, 4H, Ar-H), 7.72(s, 1H, =CH), 13.90(s, 1H, N-H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 163.5, 143.7, 116.02, 130.7, 130.4, 130.2, 115.03, 115.2. MS (ESI, *m/z*): 239 $[M+H]^+$.

*(Z)-5-(4-Nitrobenzylidene)-2-thioxothiazolidin-4-one* (**3d**): Color: Yellow crystal. Yield: 98%. M.p.: 254-256 °C. FT-IR (KBr, ν, $cm^1$): 1230 (N-C=S), 1505(-N=O, asymmetric), 1339 (N=O, symmetric). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.76 (s, 1H, =CH), 8.06 (d, 4H, Ar-H), 13.95 (s, 1H, N-H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.2, 147.5, 143.7, 141.02, 129.7, 129.4, 123.2, 123.03, 116.5. MS (ESI, *m/z*): 266 $[M+H]^+$.

*(Z)-5-(4-Hydroxybenzylidene)-2-thioxothiazolidin-4- one* (**3e**): Color: Yellow crystal. Yield: 90%. M.p.: 264-266 °C. FT-IR (KBr, ν, $cm^1$): 1175 (N-C=S), 1712 (N-C=0), 1605 (N-H), 3160 (OH). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 5.32 (s, 1H, OH), 7.63 (d, 4H, Ar-H), 7.70 (s, 1H, S=CH), 13.90 (s, 1H, N-H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 157.5, 143.7, 130.02, 130, 127.4, 115.8, 115.03, 116.2. MS (ESI, *m/z*): 238 $[M+H]^+$.




**Scheme 2**

*(Z)-5-(4-Methoxybenzylidene)-2-thioxothiazolidin-4-one* (**3f**): Color: Yellow crystal. Yield: 90%. M.p.: 246-248 °C. FT-IR (KBr, ν, cm$^{1}$): 1189 (N-C=S), 1715 (N-C=0), 1605 (N-H), 1160 (O-$CH_3$). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 3.82 (s, 3H, -$CH_3$), 7.63 (d, 4H, Ar-H), 7.70 (s, 1H, S=CH), 13.90 (s, 1H, N-H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.2, 168.5, 143.7, 169, 130.6, 130, 127.2, 116.2, 114.3, 114, 55.3. MS (ESI, *m/z*): 252 $[M+H]^+$.

*(Z)-5-(4-methylbenzylidene)-2-thioxothiazolidin-4-one* (**3g**): Color: Yellow crystal. Yield: 90%. M.p.: 220-222 °C. FT-IR (KBr, ν, cm$^{1}$): 1190 (N-C=S), 1685 (N-C=0), 1580 (N-H), 3040 (Ar-H). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.37 (s, 3H, $CH_3$), 7.51 (d, 4H, Ar-H), 7.68 (s, 1H, =CH), 13.81 (s, 1H, N-H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 136.7, 133.02, 128.7, 128.4, 127.8, 127.08, 116.2, 21.3. MS (ESI, *m/z*): 236 $[M+H]^+$.

*(Z)-5-(3-Methoxybenzylidene)-2-thioxothiazolidin-4- one* (**3h**): Color: Yellow crystal. Yield: 90%. M.p.: 226-229 °C. FT-IR (KBr, ν, cm$^{1}$): 1213(N-C=S), 1685 (N-C=O), 1585 (N-H), 3150 (Ar-H), 1165 (O-$CH_3$). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 3.82 (s, 3H, $OCH_3$), 7.08-7.65 (m, 4H, Ar-H + 1H, =CH), 13.83 (s, 1H, N-H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.1, 160, 143.2, 135.7, 129.3, 120, 116.2, 55.2. MS (ESI, *m/z*): 252 $[M+H]^+$.

*(Z)-5-(3-Methylbenzylidene)-2-thioxothiazolidin-4-one* (**3i**): Color: Yellow crystal. Yield: 92%. M.p.: 217-219 °C. FT-IR (KBr, ν, cm$^{1}$): 1190 (N-C=S), 1685 (N-C=0), 1580 (N-H), 3040 (Ar-H). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.48 (s, 3H, $CH_3$), 7.36-7.62 (m, 4H, Ar-H), 7.68(s, 1H, =CH), 13.81 (s, 1H, N-H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.5, 143.5, 138.7, 135.02, 128.8, 128.3, 126.4, 125.2, 116.03, 21.2. MS (ESI, *m/z*): 236 $[M+H]^+$.

*(Z)-5-(3-Fluorobenzylidene)-2-thioxothiazolidin-4-one* (**3j**): Color: Yellow crystal. Yield: 90%. M.p.: 199-201 °C. FT-IR (KBr, ν, cm$^{1}$): 1232 (N-C=S), 1695 (N-C=O), 1589 (N-H), 3028 (Ar-H), 1130 (C-F). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.38-7.70 (m, 4H, Ar-H), 7.71 (s, 1H, =CH), 13.83 (s, 1H, N-H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 162.5, 143.7, 136.02, 130.7, 124.4, 116.2, 114.03, 113.2. MS (ESI, *m/z*): 239 $[M+H]^+$.

*(Z)-5-(2,4-Dichlorobenzylidene)-2-thioxothiazolidin-4- one* (**3k**): Color: Yellow crystal. Yield: 90%. M.p.: 231-233 °C. FT-IR (KBr, ν, cm$^{1}$): 1230 (N-C=S), 1716 (N-C=O), 1590 (N-H), 3265 (Ar-H). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 6.63 (s, 1H, Ar-H), 7.68 (d, 2H, Ar-H), 7.85 (s, 1H, =CH), 13.95 (s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 135.7, 131.02, 130.7, 128.4, 126.2, 125.03, 115.3. MS (ESI, *m/z*): 289 $[M+H]^+$.

*(Z)-5-(2,4-Dimethoxybenzylidene)-2-thioxothiazolidin-4-one* (**3l**): Color: Yellow crystal. Yield: 95%. M.p.: 270-272 °C. FT-IR (KBr, ν, cm$^{1}$): 1235 (N-C=S), 1720 (N-C=O), 1590 (N-H), 3265(Ar-H), 1168 (O-$CH_3$). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 3.86 (s, 6H, $OCH_3$), 6.64 (s, 1H, Ar-H), 7.64 (d, 2H, Ar-H), 7.80 (s, 1H, =CH), 13.95 (s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 135.7, 129.02, 128.7, 126.4, 106.2, 107.03, 98.2, 55.02, 56.01. MS (ESI, *m/z*): 282 $[M+H]^+$.

*(Z)-5-(2-Chlorobenzylidene)-2-thioxothiazolidin-4- one* (**3m**): Color: Yellow crystal. Yield: 92%. M.p.: 179-181 °C. FT-IR (KBr, ν, cm$^{1}$): 1233(N-C=S), 1695 (N-C=O), 1590 (N-H), 850 (C-Cl), 3072 (Ar-H). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.52-7.75 (m, 4H, Ar-H + 1H, =CH), 13.96 (s, 1H, N-H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 134.7, 133.02, 127.7, 126.4, 126.2, 127.03, 116.2. MS (ESI, *m/z*): 255 $[M+H]^+$.

*(Z)-5-(Thiophen-2-ylmethylene)-2-thioxothiazolidin-4- one* (**3n**): Color: Yellow grey crystals. Yield: 90%. M.p.: 230-233 °C. FT-IR (KBr, ν, cm$^{1}$): 1235(N-C=S), 1690 (N-C=O), 1590 (N-H), 3072 (Ar-H), 668 (C-S). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.51 (s, 1H, =CH), 7.60-8.10 (m, 3H, thiophenyl), 8.07 (s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 137.5, 129.08, 129, 128.2, 122.2. MS (ESI, *m/z*): 227 $[M+H]^+$.

*(Z)-5-(Furan-2-ylmethylene)-2-thioxothiazolidin-4- one* (**3o**): Color: Brownish yellow crystals. Yield: 89%. M.p.: 223-225 °C. FT-IR (KBr, ν, cm$^{1}$): 1235(N-C=S), 1690 (N-C=O), 1594 (N-H), 3070 (Ar-H), 660 (C-O). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.53 (s, 1H, =CH), 7.62-8.10 (m, 3H, thiophenyl), 8.12 (s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ, ppm): 193.5, 168.3, 143.5, 135.7, 129.02, 128.7, 128.4, 128.2, 127.03, 116.2. MS (ESI, *m/z*): 211 $[M+H]^+$.

### *2.2.2. General method for synthesis of (Z)-5-(argio methylene)-2-(methylthio) thiazol-4(5H)-one (5)*

#### *2.2.2.1. Microwave irradiation method*

To a suspension of 5-arylidine rhodanine **3** (1 mmol), methyl iodide **4** (1.2 mmol) and triethyl amine (1.2 mmol) in water (2-3 mL) shake well and then placed in MicroSYNTH, mixture was subjected to microwave irradiation (800 W) at 40-50 °C for 3-4 min, reaction mixture were cool at room temperature. The progress of reaction was monitored by thin layer chromatography (10% chloroform:methyl alcohol). After completion of reaction solid was filtered, the residue was washed with water to afford crude product was recrystallized by ethanol to give yield 83-96% (Scheme 2 and Figure 1).

#### *2.2.2.2. Conventional stirring method*

In a small round bottom flask 5-arylidine rhodanine**3** (1 mmol), methyl iodide **4** (1.2 mmol) and triethyl amine (1.2 mmol) in water (2-3 mL), the mixture was stirred at room temperature for 60-90 min. The progress of reaction was monitored by thin layer chromatography (10% chloroform-methyl alcohol). After completion of reaction, solid was filtered, the residue was washed with water to afford crude product was recrystallized by ethanol to give yield range 70-80%. All the product are well characterized by the comparison of their spectral data (IR, $^{1}$H NMR, $^{13}$C NMR and physical properties with those reported in literature) [56].

*(Z)-5-Benzylidene-2-(methylthio)thiazol-4(5H)-one* (**5a**): Color: Yellow solid. Yield: 90%. M.p.: 146-147 °C (Lit: [56]). FT-IR (KBr, ν, cm$^{1}$): 3027 (CH-Ar) (aryl), 1696 (C=O) (Amide), 1606(C=N), 1590 (C=C), 1160(C-S), 985 (C-N). $^{1}$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.83(s,3H, S-$CH_3$), 7.44-7.76 (m, 5H, Ar-CH), 7.96 (s, 1H, =CH). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ,

ppm): 162.2 (C2), 166.9 (C4), 132.0 (C5), 151.8 (C6), 125.6-136.3 (C7-C12), 14.6 (C14). MS (ESI, *m/z*): 236 $[M+H]^+$.

*(Z)-5-(4-Chlorobenzylidene)-2-(methylthio)thiazol-4 (5H)-one* (**5b**): Color: Yellow solid. Yield: 91%. M.p.: 161-163 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3020 (CH-Ar), 1716 (C=O), 1583 (C=C), 1465 (C=N), 1155 (C-S), 979 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.82 (s, 3H, S-$CH_3$), 7.41-7.73 (m, 4H, Ar-CH), 7.98 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.2 (C2), 166.9 (C4), 132.3 (C5), 151.6 (C6), 137.9 (C7), 128.5 (C8), 128 (C9), 134.1 (C10), 128 (C11), 128.9 (C12), 14.6 (C14). MS (ESI, *m/z*): 271$[M+H]^+$.

*(Z)-5-(4-Fluorobenzylidene)-2-(methylthio)thiazol-4 (5H)-one* (**5c**): Color: Yellow solid. Yield: 90%. M.p.: 142-144 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3012 (CH-Ar), 1710 (C=O), 1597 (C=C), 1490 (C=N), 1156 (C-S), 975 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.83 (s, 3H, S-$CH_3$), 7.44-7.76 (m, 4H, Ar-CH), 7.95 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.2 (C2), 166.9 (C4), 132.4 (C5), 151.5 (C6), 130.1 (C7), 130 (C8), 115 (C9), 161.8 (C10), 152 (C11), 130.2 (C12), 14.6 (C14). MS (ESI, *m/z*): 254 $[M+H]^+$.

*(Z)-2-(Methylthio)-5-(4-nitrobenzylidene)thiazol-4 (5H)-one* (**5d**): Color: Orange solid. Yield: 96%. M.p.: 163-165 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3016 (CH-Ar), 1695 (C=O), 1590 (C=C), 1590 (C=N), 1156(C-S), 971 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.81 (s, 3H, S-$CH_3$), 2.95(s, 1H, =CH), 7.96-8.20 (m, 4H, Ar-CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.3 (C2), 166.9 (C4), 132.4 (C5), 151.7 (C6), 140.8 (C7), 129 (C8), 123 (C9), 146.8 (C10), 123 (C11), 130 (C12), 14.5 (C14). MS (ESI, *m/z*): 281 $[M+H]^+$.

*(Z)-5-(4-Hydroxybenzylidene)-2-(methylthio)thiazol-4(5H)-one* (**5e**): Color: Yellow solid. Yield: 88%. M.p.: 123-125 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3416 (OH), 3005 (CH-Ar), 1690(C=O), 1595 (C=C), 1608 (C=N), 1165 (C-S), 998 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.78 (s, 3H, S-$CH_3$), 5.47 (s, 1H, OH), 7.43-7.75 (m, 4H, Ar-CH), 7.99 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.3 (C2), 166.8 (C4), 132.5 (C5), 151.9 (C6), 127.8 (C7), 130 (C8), 115 (C9), 156.8 (C10), 115 (C11), 130 (C12), 14.3 (C14). MS (ESI, *m/z*): 252.00 $[M+H]^+$.

*(Z)-5-(4-Methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one* (**5f**): Color: Yellow solid. Yield: 90%. M.p.: 162-164 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3008 (CH-Ar), 1705 (C=O), 1578 (C=C), 1458 (C=N), 1160 (C-S), 973 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.82 (s, 3H, S-$CH_3$), 2.86 (s, 3H, O-$CH_3$), 7.43-7.76 (m, 4H, Ar-CH), 7.96 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.3 (C2), 166.6 (C4), 132.3 (C5), 152.2 (C6), 127.2 (C7), 130 (C8), 114.3 (C9), 159.3 (C10), 114.7 (C11), 130 (C12), 14.2 (C14), 54.7 (C15). MS (ESI, *m/z*): 266 $[M+H]^+$.

*(Z)-5-(4-Methylbenzylidene)-2-(methylthio)thiazol-4 (5H)-one* (**5g**): Color: Yellow solid. Yield: 89%. M.p.: 173-175 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3025 (CH-Ar), 1705 (C=O), 1595 (C=C), 1475 (C=N), 1162 (C-S), 978 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.79 (s, 3H, $CH_3$), 2.89 (s, 3H, S-$CH_3$), 7.51-7.79 (m, 4H, Ar-CH), 7.91 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.2 (C2), 166.9 (C4), 132.2 (C5), 152.7 (C6), 132 (C7), 127.8 (C8), 128.7 (C9), 137.3 (C10), 128.7 (C11), 127.8 (C12), 14 (C14), 20.9 (C15). MS (ESI, *m/z*): 250 $[M+H]^+$.

*(Z)-5-(3-Methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one* (**5h**): Color: Yellow solid. Yield: 90%. M.p.: 164-166 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3010 (CH-Ar), 1710 (C=O), 1570 (C=C), 1458 (C=N), 1158 (C-S), 975 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.81 (s, 3H, S-$CH_3$), 7.71 (s, 3H, O-$CH_3$), 7.44-7.76 (m, 4H, Ar-CH), 7.98 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.6 (C2), 166.9 (C4), 132.5 (C5), 152.7 (C6), 135 (C7), 113 (C8), 160 (C9), 113 (C10), 128.7 (C11), 120.2 (C12), 13.8 (C14), 55.2 (C15). MS (ESI, *m/z*): 266 $[M+H]^+$.

*(Z)-5-(3-Methylbenzylidene)-2-(methylthio)thiazol-4 (5H)-one* (**5i**): Color: Yellow solid. Yield: 89%. M.p.: 176-178 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3010 (CH-Ar), 1705 (C=O), 1568 (C=C), 1462(C=N), 1156 (C-S), 975 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.83 (s, 3H, S-$CH_3$), 2.41 (s, 3H, Ar-$CH_3$), 7.10-7.40 (m, 3H, Ar-CH), 7.16 (s, 1H, Ar-CH), 7.98 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.6 (C2), 166.9 (C4), 132.5 (C5), 152.7 (C6), 135 (C7), 125.3 (C8), 138 (C9), 128.2 (C10), 127.9 (C11), 124.8 (C12), 13.8 (C14), 21.6 (C15). MS (ESI, *m/z*): 250 $[M+H]^+$.

*(Z)-5-(3-Fluorobenzylidene)-2-(methylthio)thiazol-4 (5H)-one* (**5j**): Color: Yellow solid. Yield: 90%. M.p.: 144-146 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3012 (CH-Ar), 1705 (C=O), 1595 (C=C), 1468 (C=N), 1160 (C-S), 976 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.80 (s, 3H, S-$CH_3$), 7.51-7.77 (m, 3H, Ar-CH), 8.05 (s, 1H, Ar-CH), 7.96 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.3 (C2), 166.2 (C4), 132.1 (C5), 152 (C6), 135.6 (C7), 113.3 (C8), 162 (C9), 114.2 (C10), 129.9 (C11), 124.2 (C12), 13.9 (C14). MS (ESI, *m/z*): 254 $[M+H]^+$.

*(Z)-5-(2,4-Dichlorobenzylidene)-2-(methylthio)thiazol-4 (5H)-one* (**5k**): Color: Yellow solid. Yield: 90%. M.p.: 164-166 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3020 (CH-Ar), 1690(C=O), 1585(C=C), 1490 (C=N), 1168 (C-S), 965 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.83 (s, 3H, S-$CH_3$), 7.72 (s, 2H, Ar-CH), 8.01 (s, 1H, =CH), 7.46 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.3 (C2), 166.7 (C4), 132.4 (C5), 152 (C6), 131.9 (C7), 137.3 (C8), 128 (C9), 124.2 (C10), 126 (C11), 130 (C12), 13.9 (C14). MS (ESI, *m/z*): 305 $[M+H]^+$.

*(Z)-5-(2, 4-Dimethoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one* (**5l**): Color: Yellow solid. Yield: 91%. M.p.: 173-175 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3011 (CH-Ar), 1690(C=O), 1570 (C=C), 1475 (C=N), 1160 (C-S), 960 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.81 (s, 3H, S-$CH_3$), 3.86 (s, 6H, O-$CH_3$), 6.60 (s, 1H, Ar-CH), 8.05 (s, 2H, Ar-CH), 8.20 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.7 (C2), 166.8 (C4), 132.4 (C5), 152 (C6), 107.9 (C7), 142.7 (C8), 97.8 (C9), 160.2 (C10), 105.9 (C11), 130 (C12), 14 (C14). MS (ESI, *m/z*): 296 $[M+H]^+$.

*(Z)-5-(2-Chlorobenzylidene)-2-(methylthio)thiazol-4 (5H)-one* (**5m**): Color: Yellow solid. Yield: 90%. M.p.: 171-173 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3015 (CH-Ar), 1716 (C=O), 1580 (C=C), 1465 (C=N), 1156 (C-S), 976 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.81 (s, 3H, S-$CH_3$), 7.25-7.45 (m, 4H, Ar-CH), 7.99 (s, 1H, C =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 162.3 (C2), 166.4 (C4), 132.2 (C5), 152 (C6), 132.9 (C7), 134 (C8), 128.3 (C9), 129.2 (C10), 125.9 (C11), 127 (C12), 14 (C14). MS (ESI, *m/z*): 271 $[M+H]^+$.

*(Z)-2-(Methylthio)-5-(thiophen-2-ylmethylene)thiazol- 4 (5H)-one* (**5n**): Color: Yellow solid. Yield: 88%. M.p.: 151-153 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3018 (CH-Ar), 1695 (C=O), 1580 (C=C), 1490 (C=N), 1162 (C-S), 972 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.80 (s, 3H, S-$CH_3$), 6.90-8.14 (m, 3H, Ar-CH), 7.90 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 161.3 (C2), 166.3 (C4), 137.4 (C5), 151.8 (C6), 136.8 (C7), 130 (C9), 27.8 (C10), 128.9 (C11), 14 (C13). MS (ESI, *m/z*): 242 $[M+H]^+$.

*(Z)-5-(Furan-2-ylmethylene)-2-(methylthio)thiazol-4 (5H)-one* (**5o**): Color: Yellow solid. Yield: 83%. M.p.: 161-164 °C (Lit: [56]). FT-IR (KBr, ν, $cm^1$): 3016 (CH-Ar), 1695 (C=O), 1586(C=C), 1490 (C=N), 1168 (C-S), 972 (C-N). $^1H$ NMR (400 MHz, DMSO-$d_6$, δ, ppm): 2.81 (s, 3H, S-$CH_3$), 6.86-8.17 (m, 3H, Ar-CH), 7.93 (s, 1H, =CH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$, δ, ppm): 161.3 (C2), 166.3 (C4), 137.5 (C5), 151.8 (C6), 150.8 (C7), 110 (C9), 112 (C10), 142.9 (C11), 13.9 (C13). MS (ESI, *m/z*): 226 $[M+H]^+$.

## 3. Results and discussion

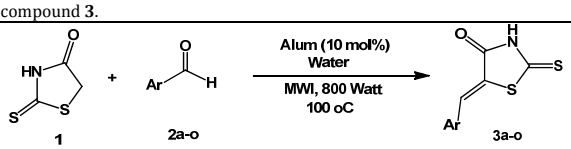
The series of reactions were performed to optimizing reaction condition in various acid, base catalysts with combination of different solvents at 40 and 100 °C programmed (800 Watt).

**Table 1.** Optimization reaction condition for the synthesis of compound **3** by microwave irradiation *.

| Entry | Base / Acid | Solvent | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | Sodium acetate | Neat | 12 | 00 |
| 2 | Sodium acetate | Water | 10 | 52 |
| 3 | Sodium acetate | Ethanol | 10 | 48 |
| 4 | Sodium acetate | Acetic acid | 10 | 93 |
| 5 | $Et_3N$ | Water | 10 | 35 |
| 6 | $Et_3N$ | EtOH | 10 | 30 |
| 7 | $Et_3N$ | Acetonitrile | 10 | 46 |
| 8 | $Et_3N$ | PEG | 10 | 48 |
| 9 | MontmorriloniteK10 | Water | 10 | 86 |
| 10 | MontmorriloniteK10 | Ethanol | 10 | 63 |
| 11 | MontmorriloniteK10 | Acetonitrile | 10 | 56 |
| 12 | MontmorriloniteK10 | PEG | 10 | 72 |
| 13 | Alum | Water | 8 | 98 |
| 14 | Alum | Ethanol | 10 | 68 |
| 15 | Alum | Acetonitrile | 10 | 60 |
| 16 | Alum | PEG | 10 | 76 |

* Reaction condition: (Microwave assisted) rhodanine (1 mmol), aldehyde (1 mmol) and alum (10 mol%) in water at 100 °C, 800 Watt.

**Table 2.** Microwave assisted synthesis of compound **3**.




| Entry | Compound | Ar | Time (min) | M.p. (°C) | Yield (%) * |
|---|---|---|---|---|---|
| 1 | 3a | Benzyl | 2 | 203-205 | 90 |
| 2 | 3b | 4-Chlorobenzyl | 3 | 130-132 | 91 |
| 3 | 3c | 4-Flurobenzyl | 3 | 225-227 | 90 |
| 4 | 3d | 4-Nitrobenzyl | 2 | 254-256 | 98 |
| 5 | 3e | 4-Hydroxybenzyl | 4 | 264-266 | 90 |
| 6 | 3f | 4-Methoxybenzyl | 3 | 246-248 | 90 |
| 7 | 3g | 4-Methylbenzyl | 3 | 220-222 | 90 |
| 8 | 3h | 3-Methoxybenzyl | 3 | 226-229 | 90 |
| 9 | 3i | 3-Methylbenzyl | 3 | 217-219 | 92 |
| 10 | 3j | 3-Flurobenzyl | 3 | 199-201 | 90 |
| 11 | 3k | 2,4-Dichlorobenzyl | 3 | 231-233 | 90 |
| 12 | 3l | 2,4dimethoxybenzyl | 3 | 270-272 | 95 |
| 13 | 3m | 2-Chlorobenzyl | 3 | 179-181 | 92 |
| 14 | 3n | 2-Thiophenyl | 3 | 230-233 | 90 |
| 15 | 3o | 2-Furyl | 3 | 223-225 | 89 |

* Isolated yield after purification by MeOH-$CHCl_3$.

**Table 3.** Optimization reaction condition for the synthesis of compound **5** [a].

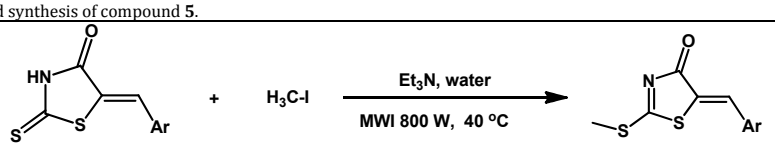
| Entry | Base | Solvent | Time (min) | Yield (%) [b] |
|---|---|---|---|---|
| 1 | $K_2CO_3$ | Neat | 5 | 00 |
| 2 | $K_2CO_3$ | Water | 4 | 60 |
| 3 | $Na_2CO_3$ | Neat | 5 | 00 |
| 4 | $Na_2CO_3$ | Water | 4 | 40 |
| 5 | NMP | Neat | 5 | 00 |
| 6 | NMP | Water | 4 | 65 |
| 7 | $Et_3N$ | Neat | 5 | 00 |
| 8 | $Et_3N$ | Water | 2 | 96 |
| 9 | $Et_3N$ | EtOH | 2 | 40 |
| 10 | $Et_3N$ | EtOH:Water (1:1) | 3 | 58 |
| 11 | $Et_3N$ | MeOH | 3 | 30 |
| 12 | $Et_3N$ | $CH_3CN$ | 2 | 73 |
| 13 | $Et_3N$ | $CH_2Cl_2$ | 2 | 78 |
| 14 | $Et_3N$ | DMF | 2 | 56 |

[a] Reaction condition: 5-arylidine rhodanine (1 mmol), methyl iodide (1.2 mmol) and triethyl amine (1.2 mmol) in water (2-3 mL) at 40 °C.
[b] Isolated yield after purification by recrystallization from ethanol. TLC (10% chloroform: methanol).

In first model reaction of chalcone formation of rhodanine (1 mmol) and aryl aldehyde (1 mmol) in presence of various mole% of alum (5/10/15 mol %) and minimum amount of different solvent (Table 1), in finding Alum (10 mol %) with water or in acetic acid-sodium acetate (buffer solution) gave better yield (Table 1, entry 13, 4) among these alum water was proven good catalyst solvent combination (Table 1, entry 13). Thus, all example were tested in alum-water and excellent yield was obtained (89-98%) in short reaction time (Table 2).

In second model reaction of S-methylation of benzylidine rhodanine (1 mmol), Iodomethane (1.2 mmol) in presence of triethyl amine (1.2 mmol) and water (2-3 mL) gave excellent yield in very less time of reaction at 40 °C temperature, among the compared catalyst solvent combination (Table 3, entry 8) this is due to triethyl amine water is best paired emerged base catalyst-solvent. Thus, we decided all reaction carried out in triethyl amine-water. All example were tested reasonably good to excellent yields (83-96%) could be achieved in short reaction time 2-4 min (Table 4). Without solvent, reaction did not detect as fruitful one (Table 3, entry 7). An electronic effect was observed, electron withdrawing groups (Table 4, entry 2-4, 10, 11, 13) and unsubstituted aldehyde (Table 4, entry 1) were well tolerate. Five and six member heterocyclic aryl aldehyde gave corresponding yield (Table 4, entry 14, 15).

**Table 4.** Microwave assisted synthesis of compound **5**.




3 4 5a-o

| Entry | Compound | Ar | Time (min) | M.p. (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 5a | Benzyl | 2 | 146-148 | 90 |
| 2 | 5b | 4-Chlorobenzyl | 3 | 161-163 | 91 |
| 3 | 5c | 4-Flurobenzyl | 3 | 142-145 | 90 |
| 4 | 5d | 4-Notrobenzyl | 2 | 163-165 | 96 |
| 5 | 5e | 4-Hydroxybenzyl | 4 | 123-125 | 88 |
| 6 | 5f | 4-Methoxybenzyl | 3 | 162-164 | 90 |
| 7 | 5g | 4-Methylbenzyl | 3 | 173-175 | 89 |
| 8 | 5h | 3-Methoxybenzyl | 3 | 164-166 | 90 |
| 9 | 5i | 3-Methylbenzyl | 3 | 176-178 | 89 |
| 10 | 5j | 3-Flurobenzyl | 3 | 144-146 | 90 |
| 11 | 5k | 2,4-Dichlorobenzyl | 3 | 164-167 | 90 |
| 12 | 5l | 2,4-Dimethoxybenzyl | 3 | 173-175 | 91 |
| 13 | 5m | 2-Chlorobenzyl | 3 | 171-173 | 90 |
| 14 | 5n | 2-Thiophenyl | 3 | 151-153 | 88 |
| 15 | 5o | 2-Furyl | 3 | 161-164 | 83 |

Finally, the structure of compounds were substantiated by $^1$H NMR spectra, only one signal for the methyne proton in the range δ 7.81-7.96 ppm, at lower field values than those expected for the *E*-isomers. This strongly indicates that the compounds have the *Z*-configuration. IR spectrum showed a strong absorption band at 1690-1698 cm$^{-1}$ due to a carbonyl group of amide.

## 4. Conclusion

In conclusion, we have successfully developed an eco-friendly synthesis route of 5-substituted (aryl/hetero-aryl)-2-(methylthio)-thiazolones using easily available, alum as catalyst and water as green solvent in good to excellent yield of the products. Notable advantages for the present protocol include short reaction time, cleaner reaction profile and easy isolation of product by microwave irradiation technique using green catalyst and solvent. An effort toward the synthesis of other important drug molecules with a rhodanine moiety by microwave irradiation, ultrasonication method is ongoing in our laboratory.

### *Acknowledgements*

The authors are thankful to Principal and Head, Department of Chemistry, Sant Ramdas College, Ghansawangi, Dist. Jalna affiliated to Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, 431004 (MS), India for providing financial assistance for instrument help.

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