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## Green condensation reaction of aromatic aldehydes with rhodanine catalyzed by alum under microwave irradiation

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### ABSTRACT

An efficient one pot alum catalyzed, microwave enhanced, clean process for the synthesis of 5-arylidenerhodanines by the Knoevenagel condensation of aromatic aldehydes with rhodanine in aqueous media is described. Only 15 mole % of alum is enough in this protocol to achieve optimal yields and this protocol is fairly general and applicable to aromatic aldehydes. The use of alum, water and MW has promising reaction response, such as short reaction time, excellent product yields, and simple work-up of the products makes the reaction convenient, more economic, and environmentally benign.

**Key words:** Microwave irradiation, Rhodanine, Alum catalyst

### INTRODUCTION

Heterocyclic chemistry is of great importance to the medicinal chemists because the steady growth of interest in heterocyclic compounds is connected with their therapeutic activity. Further, the compounds containing the 2-thioxothiazolidin-4-one ring (rhodanine derivatives) have demonstrated wide range of pharmacological activities, which include antimicrobial [1-3], antiviral [4], antidiabetic [5] and anticancer activity [6]. Additionally, rhodanine-based molecules have been popular as small molecule inhibitors of numerous targets such as HCV NS5B protease [7], HCV NS3 protease [8], aldose reductase [9],  $\beta$ -lactamase [10], UDP-*N*-acetylmuramase/*L*-alanine ligase [11], fungal protein mannosyl transferase-1 (PMT1) [12], cathepsin-D [13], anthrax lethal factor protease [14], histidine decarboxylase [15], JNK-stimulating phosphatase-1 (JSP-1) [16] and phosphodiesterase (PDE-4) [17]. Among the thiazolidine derivatives, numerous compounds containing thiazolidine-2,4-dione and rhodanine have been recognized as new potential anticancer agents. For example, GSK1059615 is a potent, reversible, ATP-competitive, thiazolidinedione inhibitor of PI3K  $\alpha$  [18-19].

Now-a-days one pot reactions are gaining prominence due to their environmental advantages and cost effectiveness. Microwave mediated synthesis in organic chemistry reaching a stage of importance because of its proven ability to accelerate even very robust transformations [20]. Biological activities associated with rhodanines and as a part of our research interest in the development of multifunctional libraries of rhodanine, therefore it was felt worthwhile to study these reactions in presence of alum under microwave conditions with the aim of decreasing the reaction time and increasing the yield. Alum ( $KAl(SO_4)_2 \cdot 12H_2O$ ) is a cheap, non-toxic, inexpensive, eco-friendly, and easy handling catalyst and found use in various organic reactions such as in the synthesis of dihydropyrimidines via Biginelli [21], coumarins [22], *cis*-isoquinolonic acids [23], 1,3,4-oxadiazoles [24], 1,5-benzodiazepines [25],

dibenzoxanthines [26], trisubstituted imidazoles [27], 2,3-dihydroquinazolin-4(1H)-ones [28],  $\alpha\beta$ -unsaturated acids [29] and 5-arylidene-2,4-thiazolidinedione[30] were reported.

In continuation of our work on the synthesis of 5-arylidenerhodanines [31] using microwave irradiation, herein we wish to report the alum catalyzed, microwave assisted synthesis of 5-arylidenerhodanines.

### MATERIALS AND METHODS

All the chemicals and solvents were analytical grade and used without further purification. Melting points were determined on open capillaries, using Boitus melting point apparatus, expressed in °C and are uncorrected.  $^1\text{H}$  NMR spectra of the compounds were recorded on Bruker AMX-400 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in  $\delta$  ppm. Infrared spectra were recorded in KBr disc on Bruker ALPHA-T FTIR spectrophotometer. The mass spectrum of the compounds were recorded either on Agilent-1100 ESI-Mass (Turbo Spray) Spectro photometer. Microanalyses were carried out with a Perkin-Elmer model-2400 series II apparatus and were within  $\pm 0.4\%$  of the theoretical values. Column chromatography was performed on silica gel (230-400 mesh).

#### General procedure for the synthesis of 5-arylidenerhodanines ( $\text{C}_1$ - $\text{C}_{11}$ ) by Knoevenagel condensation:

A mixture of rhodanine **1** (20 mmol), respective aromatic aldehyde **2** (20 mmol) and  $\text{NH}_2\text{SO}_3\text{NH}_4$  (ammonium sulphamate) was subjected to microwave irradiation (MWI) at 600 watts intermittently at 30 sec intervals for specific time (3-6 min) (Scheme 1). Completion of the reaction was identified by TLC using silica gel-G. After completion of the reaction, the mixture was poured onto crushed ice, and the solid that separated was isolated by filtration, dried and recrystallized from ethanol to give desired product ( $\text{C}_1$ -  $\text{C}_{11}$ ). The physical and spectral characterization data represented in Table 1 and 2.

### RESULTS AND DISCUSSION

#### Chemistry

As a part of the continued interest to develop efficient protocols for the synthesis of biologically active molecular scaffolds via one-pot multicomponent reactions, herein is reported a highly efficient alum catalyzed synthesis of 5-arylidene rhodanines by reacting rhodanine and aromatic aldehydes using alum as catalyst and water as solvent by employing microwave energy (Scheme I). In order to optimize the reaction conditions, a typical reaction of rhodanine and benzaldehyde were studied by varying catalyst concentration, solvent, MW power, temperature and time; the results are given in Table 1. The reaction under conventional conditions using 15 mol % of alum in water under reflux for 2 hr gave rise to 78% yield of the product 5-arylidenerhodanine **C1**. However, when the reaction was subjected to microwave irradiation in domestic microwave, it gave rise to the product **C1** with 94% yield in 10 min (Table 1, entry 4). In the absence of the catalyst, however, product is formed with low yield under MW conditions (Table 1, entry 1). Changing the concentration of alum to 5, 10, 15, and 20 mol %, gave rise to 66, 71, 94, and 90% yields of 4a respectively (Table 1, entries 2, 3, 4 and 5). Therefore, 15 mol % of alum was concluded to be the optimum catalyst concentration to push the desired reaction to the maximum possible extent. In order to check the effect of MW power, the model reaction using 15 mol % of alum was also undertaken at 200 W and 400 W affording 82% and 94% yields respectively. Further enhancement in microwave power did not improve the product yield. With a view to examine the solvent effect, the reaction was carried out in methanol and ethanol (Table 1, entries 6, 7, 8 and 9) in addition to water. In addition, it was found that the solvent played a crucial role in this reaction. Methanol and ethanol as solvents were also able to facilitate the Knoevenagel reaction. Water was found to be the most suitable solvent for this reaction, due to the solubility of alum in water. Thus, 400 W microwave powers in water were adopted as the optimum reaction condition for the subsequent reactions. Under the optimized set of reaction conditions, a number of 5-arylidenerhodanines have been synthesized in excellent yields in 6-12 min using a variety of aromatic aldehydes (Table 2). The purity of the compounds was checked by TLC and elemental analyses. Both analytical and spectral data ( $^1\text{H}$ -NMR) of all the synthesized compounds were in full agreement with proposed structures. The  $^1\text{H}$  NMR spectra of the 5-arylidenerhodanines revealed the characteristic methylenic proton in between  $\delta$  7.1 and 7.94. The spectra also showed the peaks accounting for the aromatic protons and for the different substituents present in between the corresponding regions of the spectrum. The spectra characterization data is given in Table 3.

Herein, we have developed an efficient and green method for one pot synthesis of 5-arylidenerhodanines has been achieved by two component Knoevenagel condensation reaction of aromatic aldehyde and rhodanine using alum as catalyst in water. The method makes use of commercially available and inexpensive starting materials and offers several advantages, such as avoiding toxic solvent or catalyst, simple work-up procedure, avoiding chromatographic purification, and improved yields. In this methodology, the products are isolated in pure form by simple filtration and as a result of which yield losses are avoided during workup. To investigate the generality of the reaction various substituted and unsubstituted aromatic aldehydes with electron withdrawing substituents also reacted smoothly with short reaction time and with excellent yield without any byproduct. It is believed that many therapeutically active molecules could be synthesized by this environmentally friendly multicomponent approach.

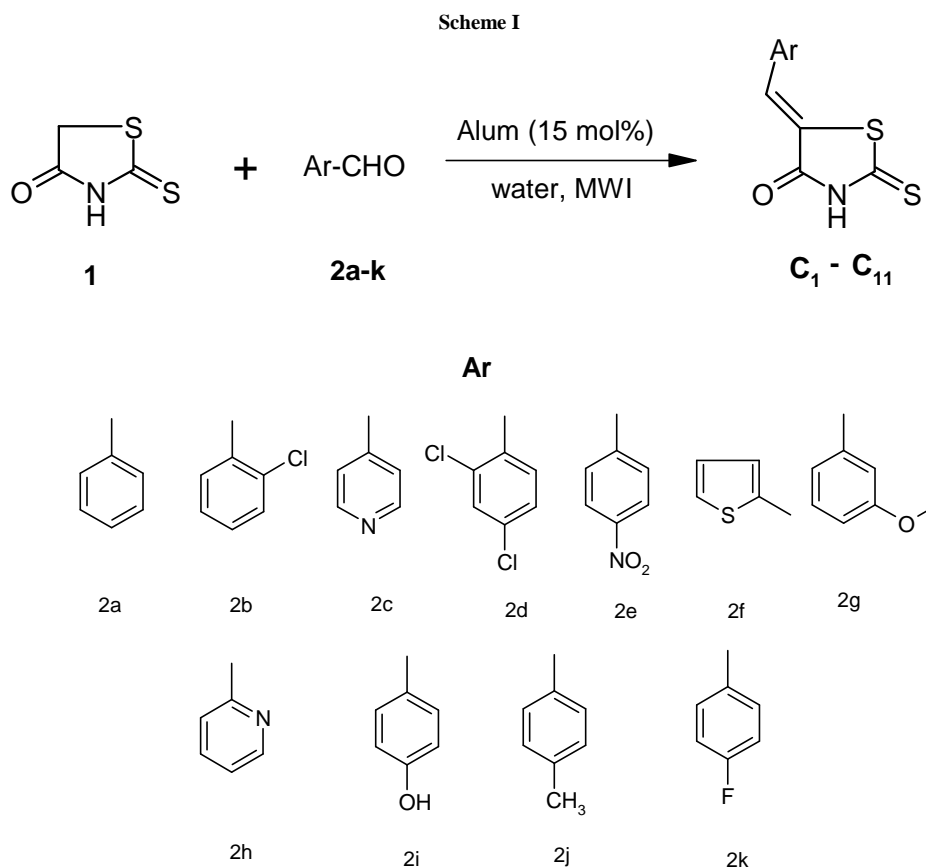


Table 1. Optimization of reaction conditions for MW- assisted synthesis of C1

| Entry | Catalyst (mol%) | Solvent  | MW (W) | Time (min) | Yield (%) <sup>a</sup> |
|-------|-----------------|----------|--------|------------|------------------------|
| 1.    | ---             | water    | 400    | 60         | 25                     |
| 2.    | 5               | water    | 400    | 10         | 66                     |
| 3.    | 10              | water    | 400    | 10         | 71                     |
| 4.    | 15              | water    | 400    | 10         | 94                     |
| 5.    | 20              | water    | 400    | 10         | 90                     |
| 6.    | 15              | methanol | 400    | 10         | 52                     |
| 7.    | 20              | methanol | 400    | 10         | 54                     |
| 8.    | 15              | ethanol  | 400    | 10         | 58                     |
| 9.    | 20              | ethanol  | 400    | 10         | 63                     |
| 10.   | 15              | water    | ---    | 10         | 78                     |

a: Isolate yield

Table 2. Microwave assisted synthesis of 5-arylidenerhodanines catalyzed by alum in water

| Compound        | Aldehyde           | Time (min) | Yield (%) <sup>a</sup> | m.p. [Lit.] °C         |
|-----------------|--------------------|------------|------------------------|------------------------|
| C <sub>1</sub>  | phenyl             | 10         | 94                     | 208 [208-210] (Ref 31) |
| C <sub>2</sub>  | 2-chlorophenyl     | 8          | 95                     | 230 [230-232] (Ref 31) |
| C <sub>3</sub>  | 4-pyridyl          | 9          | 85                     | 294 [290-292] (Ref 31) |
| C <sub>4</sub>  | 2,4-dichlorophenyl | 6          | 92                     | 216 [232-234] (Ref 31) |
| C <sub>5</sub>  | 4-nitrophenyl      | 8          | 90                     | 244 [240-242] (Ref 31) |
| C <sub>6</sub>  | 2-thienyl          | 11         | 86                     | 252 [250-252] (Ref 31) |
| C <sub>7</sub>  | 3-methoxyphenyl    | 12         | 88                     | 247 [244-246] (Ref 31) |
| C <sub>8</sub>  | 2-pyridyl          | 10         | 86                     | 262 [262-264] (Ref 31) |
| C <sub>9</sub>  | 4-hydroxyphenyl    | 8          | 85                     | 197 [196-198] (Ref 31) |
| C <sub>10</sub> | 4-methylphenyl     | 10         | 82                     | 244 [146-248] (Ref 31) |
| C <sub>11</sub> | 4-fluorophenyl     | 7          | 95                     | 238 [236-238] (Ref 31) |

Table 3: Spectral data of 5-arylidenerhodanines (C<sub>1</sub>-C<sub>11</sub>)

| Compound        | IR in KBr cm <sup>-1</sup>  | <sup>1</sup> H-NMR (CDCl <sub>3</sub> / TMS) δ ppm  |
|-----------------|---|---|
| C <sub>1</sub>  | 1234 (N-C=S), 1697 (N-C=O), 1586 (N-H), 3054 (Ar-CH)  | 7.65(1H, s, =CH), 7.50-7.67 (5H, Ar-H), 13.85 (1H, s, N-H).                                     |
| C <sub>2</sub>  | 1233 (N-C=S), 1696 (N-C=O), 1589 (N-H), 3072 (Ar-CH), 849 (C-Cl)                                    | 7.67 (1H, s, =CH), 7.53-7.77 (4H, Ar-H), 13.96 (1H, s, N-H).                                    |
| C <sub>3</sub>  | 1242 (N-C=S), 1700 (N-C=O), 1596 (C=N), 3014 (Ar-CH)  | 7.58 (1H, s, =CH), 7.54-8.74 (4H, Ar-H).  |
| C <sub>4</sub>  | 1227 (N-C=S), 1696 (N-C=O), 1579 (N-H), 3100 (Ar-CH)  | 7.85 (1H, s, =CH), 7.54-7.86 (3H, Ar-H), 13.99 (1H, s, N-H).                                    |
| C <sub>5</sub>  | 1228 (N-C=S), 1716 (N-C=O), 1597 (N-H), 3265 (Ar-CH), 1505 (N=O, asymmetric), 1339 (N=O, symmetric) | 7.75 (1H, s, =CH), 7.75-8.36 (4H, m, Ar-H), 13.98 (1H, s, NH).                                  |
| C <sub>6</sub>  | 1186 (N-C=S), 1680 (N-C=O), 1578 (N-H), 3056 (Ar-CH), 665 (C-S)                                     | 7.94 (1H, s, =CH), 7.32-8.10 (3H, Heteroaryl-H), 13.80 (1H, s, N-H).                            |
| C <sub>7</sub>  | 1213 (N-C=S), 1685 (N-C=O), 1584 (N-H), 3154 (Ar-CH), 1166 (O-CH <sub>3</sub> )                     | 7.4 (1H, s, =CH), 7.08-7.63 (4H, m, Ar-H), 3.82 (3H, s, OCH <sub>3</sub> ), 13.83 (1H, s, N-H). |
| C <sub>8</sub>  | 1233 (N-C=S), 1715 (N-C=O), 1596 (C=N), 3113 (Ar-CH)  | 7.67 (1H, s, =CH), 7.42-8.8 (4H, Heteroaryl-H), 13.6 (1H, s, N-H).                              |
| C <sub>9</sub>  | 1173 (N-C=S), 1712 (N-C=O), 1603 (N-H), 3160 (OH)   | 7.7 (1H, s, =CH), 7.48-7.83 (4H, m, Ar-H), 13.91 (1H, s, N-H).                                  |
| C <sub>10</sub> | 1185 (N-C=S), 1686 (N-C=O), 1578 (N-H), 3039 (Ar-CH)  | 7.57 (1H, s, =CH), 7.36-7.62 (4H, m, ar-H), 2.37 (3H, s, CH <sub>3</sub> ), 13.81 (1H, s, N-H). |
| C <sub>11</sub> | 1235 (N-C=S), 1694 (N-C=O), 1580 (N-H), 3023 (Ar-CH), 1120 (C-F)                                    | 7.65 (1H, s, =CH), 7.38-7.70 (4H, m, ar-H), 13.82 (1H, s, NH).                                  |

## CONCLUSION

In the present study we have demonstrated a simple, efficient and cleaner strategy for the synthesis of 5-arylidenerhodanines by Knoevenagel condensation of different aromatic aldehydes with rhodanine in presence of alum in water by employing microwave irradiation power. Moreover, the catalyst used is easily available, inexpensive, non-toxic, eco-friendly, facile work-up, which makes the reaction convenient, more economic, and environmentally benign. The products are obtained in much shorter time as compared to the conventional method with increase in the yield from 4-23%. The quality of products is also found to be better as compared to the conventional method.

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