An eco-friendly solvent free one pot multi-component synthesis of Coumarin thiazolidinone derivatives

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ABSTRACT

8-ethoxy-3-acetyl coumarin 1, thiosemicarbazide 2 was condensed under microwave irradiation gives 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazinecarbothioamide 3 then 3, chloroacetyl chloride 4, substituted aryl aldehydes 5, were condensed in presence of alum catalyst to formed 5-benzylidene-2-((E)-(1-(8-ethoxy-2-oxo-2H-chromen-3yl)ethylidene)hydrazono) thiazolidin-4-one 6, by simple grinding technique at room temperature under solvent free condition. Synthesized compounds were confirmed by IR, NMR, Mass and CHN analysis.

Keywords: Coumarin thiazolidinone, Green Synthesis, Knoevenagel condensation reaction.

INTRODUCTION

Heterocyclic compounds widely occur in nature and are essential to life. In particular, Coumarin and its derivatives are used as additives in food, perfumes, cosmetics, pharmaceuticals, agrochemicals [1, 2], for their cardiothioc, anticancer, antiviral, properties [3, 4] and as laser dyes in the blue-green region. These types of dyes have been employed as labels for fluorescent energy transfer experiments [5, 6]. Coumarin compounds also form number of drugs, which are widely used in medicine as anticoagulant, anti arrhythmic, hypertensive and immune modulant agents [7].

Coumarin thiazolidinone derivatives plays an important role in chemistry, which is used as antifungal, antioxidant [8], antimicrobial [9], in -vivo cytotoxicity evaluation [10], antimicrobial [11] anticonvulsant and analgesic agent [12], Antitumor [13], antibacterial [14], anti-inflammatory [15] In our continuation of our research interest thiosemicarbazide moiety [16].

The application of solvent-free reaction conditions in organic chemistry has been explored extensively within the last decade. It was shown to be an efficient technique for various organic reactions. solvent-free conditions often lead to a remarkable decrease in reaction time, increased yields, easier workup, and in some cases enhancement of regio and stereo selectivity [18].
Alum [KAl(SO4)2.12H2O] has been found to be effective in the synthesis of cis-isoquinolic acids [19a], mono and disubstituted 2,3-dihydroquinazolin-4(1H)-ones[19b], dihydropyrimidines via Biginelli reaction [19c] coumarins [19d],1,3,4-oxadiazoles [19e], dibenzoanthenes [19f], 1,5-benzodiazepines[19g], and trisubstituted imidazoles [19h].

Many research study reported for green grinding method with formation of carbon carbon or carbon heteroatom single as well as double bond, some of name reactions example is Grignard [20], Reformatsky [21], Dieckmann [22], Aldol reaction [23] and various other coupling type of reactions [24-26]. An environmentally benign process are requested for crucial perventation of pollution, enviro-economic factors, low cost and simplicity in processing these factors are beneficial to industries as well as environment [27]. However, there are no examples of the use of ‘alum as a catalyst under solvent free grinding technique,’ for the synthesis of Coumarin thiazolidinone derivatives, thus we choose environmentally benign process.

**MATERIALS AND METHODS**

All the compounds used in synthesis were of analytical grade, the melting points of the compounds were determined in open head capillary and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm⁻¹ by using KBr pallet on FT-IR Perkin spectrophotometer. H¹ NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in DMSO-d₆. The values of chemical shift are expressed in δ ppm as a unit. All the compounds were checked for purity by thin layer chromatography (TLC).

**REACTION SCHEME:**

![Reaction Scheme](image-url)
1. General Procedure for synthesis of 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazine carbothioamide 3 by microwave irradiation technique:
An equimolar amount of mixture of 8-ethoxy-3-acetyl coumarin (10 mmol) and thiosemicarbazide (10 mmol) in 10 mL of DMF was subjected to microwave irradiation for 4-5 min. at 400W. The progress reaction was monitored by TLC. After completion of reaction filtered off, washed with alcohol dried and recrystallised from ethyl alcohol, colorless needles was obtained (yield 86%) melting point range 216-222°C

2. General Procedure for synthesis of 5-benzylidene-2-(E)-(1-(8-ethoxy-2-oxo-2H-chromen-3yl) ethylidene) hydrazono thiazolidin-4-one 6 by grinding technique techniques:
An equimolar amount of mixture of 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazine carbothioamide 3 (5 mmol), chloroacetyl chloride 4 (5mmol), substituted aryl aldehydes 5 (5mmol) and 15 mol% of alum [KAl(SO₄)₂ 12H₂O] was grind in mortar by pestle for 8-15min. The progress reaction was monitored by TLC. After completion of reaction filtered off, washed with alcohol dried and recrystallised from ethyl alcohol, Pale yellow color product 6 was obtained (yield 80%) melting point 221°C

Table 1. Optimization of catalyst with respect to yield and time:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Catalyst</th>
<th>Mole %</th>
<th>Yield (%)</th>
<th>Time (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acetic acid</td>
<td>15</td>
<td>80/10</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Boric acid</td>
<td>15</td>
<td>60/15</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Oxalic acid</td>
<td>15</td>
<td>20/15</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Sodiumacetate-acetic acid</td>
<td>15</td>
<td>89/10</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Ammonium-acetate-acetic acid</td>
<td>15</td>
<td>70/15</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Pyridine-acetic acid</td>
<td>15</td>
<td>81/15</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Alum</td>
<td>20</td>
<td>96/12</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Alum</td>
<td>10</td>
<td>80/15</td>
<td></td>
</tr>
</tbody>
</table>

*Isolated yield

Table 2. Synthesis of 5-benzylidene-2-(E)-(1-(8-ethoxy-2-oxo-2H-chromen-3yl) ethylidene) hydrazono thiazolidin-4-one 6

![Scheme 2](image)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Compound R (Substituent)</th>
<th>Isolated yield(/%)/Time(min.)</th>
<th>Melting Point (°C)</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>6a H</td>
<td>99/15</td>
<td>200-214</td>
<td>Brown</td>
</tr>
<tr>
<td>2.</td>
<td>6b 4-OCH₃</td>
<td>96/08</td>
<td>218-222</td>
<td>Pale brown</td>
</tr>
<tr>
<td>3.</td>
<td>6c 2,4(OCH₃)₃</td>
<td>91/10</td>
<td>218-223</td>
<td>Light brown</td>
</tr>
<tr>
<td>4.</td>
<td>6d 4-CH₃</td>
<td>86/12</td>
<td>199-205</td>
<td>Colorless</td>
</tr>
<tr>
<td>5.</td>
<td>6e 4-CH₂</td>
<td>92/10</td>
<td>243-247</td>
<td>Colorless</td>
</tr>
<tr>
<td>6.</td>
<td>6f 4-CN</td>
<td>89/10</td>
<td>221-226</td>
<td>Pale brown</td>
</tr>
<tr>
<td>7.</td>
<td>6g 4-Cl</td>
<td>83/15</td>
<td>217</td>
<td>Light brown</td>
</tr>
<tr>
<td>8.</td>
<td>6h 4-NO₂</td>
<td>81/12</td>
<td>240-250</td>
<td>Light yellow</td>
</tr>
<tr>
<td>9.</td>
<td>6i Furfyl(C₆H₅)</td>
<td>78/15</td>
<td>-</td>
<td>Brown grey</td>
</tr>
<tr>
<td>10.</td>
<td>6j 3-NO₂</td>
<td>83/15</td>
<td>226-229</td>
<td>Light yellow</td>
</tr>
</tbody>
</table>

Reaction condition: 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazine carbothioamide (5 mmol), chloroacetyl chloride (5mmol), substituted aryl aldehydes (5mmol) and alum 15mol%
Possible mechanism:

Spectral data for compound (3) and (6):

**2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazinecarbothioamide 3** by grinding technique (3):

IR (KBr) v (cm⁻¹): 3404, 3254, 3178, (NH andNH₂), 2979 (C-H aliphatic), 1729 (CO); ¹H-NMR (DMSO-d₆) δ: 8.54 (s, 2H), 7.02 (s, 1H), 2.04 (s, 3H), 7.52 (s, 1H), 7.39 (d, 1H), 7.37 (t, 1H), 7.17(d, 1H), 4.02 (qt., 2H), 1.30 (t, 3H)

MS m/z (%): 305 (M⁺, 42), 290 (100), 245 (23), 230 (27), 161 (24); Anal. calcd. for C₁₃H₁₅N₃O₆: C, 55.07; H, 4.95; N, 13.76; found: C, 55.09; H, 4.94; N, 13.78%.

**5-benzylidene-2-(E)-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-5-(4-methoxybenzylidene)thiazolidin-4-one 6b:**

IR (KBr) v (cm⁻¹): 2941 (CH aliphatic), 1685-1705 (CO), 1605 (N=C); ¹H-NMR (DMSO-d₆) δ: 1.45 (t, 3H, CH₃, J = 6.8Hz), 2.35 (s, 3H, CH₃), 3.83 (s, 3H, OCH₃), 4.20 (q, 2H, CH₂, J = 6.7Hz), 7.56–7.81 (m, 7H, Ar-H), 8.29 (s, 1H, =CH-Ar), 8.42(s, 1H, 4-H), 12.43 (brs, 1H, NH); Anal. calcd. for C₂₅H₂₁N₃O₆: C, 62.19; H, 4.57; N, 9.05; found: C, 62.18; H, 4.58 N, 9.09%.

RESULTS AND DISCUSSION

Initially, simple condensation reaction carried out between acetyl coumarin and thiosemicarbazide in microwave irradiation expeditious obtained hydrazinecarbothioamide 3 Scheme 1 We optimized or screened of catalyst in a constant amount of mol % (15 mol%) for this multicomponent reaction of 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazinecarbothioamide3 (5 mmol), chloroacetyl chloride 4 (5mmol), substituted aryl aldehydes 5 (5mmol) an excellent yield was obtained (Table 1. Entry 7 as well as entry no.4 and 1), if we increased mole% of alum catalyst there is no too effect on the yield of product. (Table 1, entry no 8) gradually decreases yield of product in entry no. 9.

The optimum conditions for the multicomponent synthesis of Coumarin thiazolidinone derivatives required the use of alum (15 mol%), simple grinding technique using the optimized reaction conditions, the scope and generality of this reaction were investigated (Table 2, Scheme 2). an aromatic aldehydes with different functional groups such as hydroxyl, chloro, nitro methoxy, nitrile etc. were applied in the reaction, we observed that electronic effects on the
aldehydes had little influence on the yield and reaction time: arylaldehydes with electron-donating groups reacted rapidly, gives better yield (Table 2, entry no.2) than unsubstituted aryl aldehyde (Table 2, entry no.1.), the poor yield was obtained for electron withdrawing substituted aryl aldehyde. summarized in Table 2,entry 6,7,8,9,10. On the basis of the results obtained from Table 2. and according to proposed mechanism in Scheme 2,for the formation of Coumarin thiazolidinone derivatives

In all the cases, the Coumarin thiazolidinone derivatives precipitated under solvent free were obtained in excellent yields after recrystallization from ethanol. No side products were observed during the course of the reaction; thus we believed that the present methodology opens new possibilities for the green synthetic organic chemistry and could be an important addition to existing methodologies, in our experiments, the completion of reaction was confirmed by the disappearance of the starting on TLC and the structure of compounds (6a-k) were substantiated by IR, $^1$HNMR and CHN analysis, The IR spectrum of representative compound 6, shows a strong absorption band at the region 1685-1705 cm$^{-1}$ which is due to a carbonyl group thiazolidinone moiety. $^1$HNMR spectra of compound 6 shows one singlet for the methylene proton (1H) in the range $\delta$ 8.26-8.31 ppm. and another one signal for the methylene proton (1H) $\delta$ 12.40 ppm (-NH) and another $\delta$ values. Thus conformed that coumarin thiazolidinone compound.

**CONCLUSION**

In conclusion, we have developed a convenient alum-catalyzed synthetic protocol for Coumarin thiazolidinone derivatives; an alum is commercially available and inexpensive. The time required for the completion of the reaction is obviously reduced and the yields of the products are increased. Hence, this route is economical and eco-friendly when compared to some of the other existing methods. An effort toward the synthesis of other important drug molecules with azoles moiety by grinding as well as microwave irradiation method is 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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**REFERENCES**


