Zinc chloride-catalyzed one-pot synthesis of 3-[2-(3-methyl-4,5-dihydro-furo[2,3-c]-pyrazol-1-yl)thiazol-4-yl]-chromen-2-ones via a three component reaction

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A simple and convenient procedure for the synthesis of 3-[2-(3-methyl-4,5-dihydro-furo[2,3-c]-pyrazol-1-yl)-thiazol-4-yl]-chromen-2-ones via a three component reaction is described through anhydrous zinc chloride-catalyzed one pot condensation of 3-(2-bromoacetyl)coumarin, thiosemicarbazide and 2-acetylbutyrolactone in good yields. The title compounds are also synthesized via an alternative procedure.

Keywords: 2-Acetylbutyrolactone, thiazole, pyrazole, benzopyran-2-one, 4,5-dihydrofuropyrazole, one-pot synthesis

Coumarins occur extensively in the plant kingdom, and many of them exhibit a variety of biological activity such as anthelmintic, anticoagulant, hypnotic and insecticide activities. Various simple and 3-substituted coumarins have been isolated from natural sources. Coumarins bearing a heterocyclic moiety at 3rd position are uricosuric and CNS active agents, further thiazoles and also coumarin derivatives with a heterocyclic system at 3rd position exhibit promising biological activities. A literature survey revealed that thiazoles are generally prepared by Hantzsch thiazole synthesis from α-halo ketones and thioureas and thioamides.

Later King et al. and other workers synthesized amino thiazoles by replacing α-halo ketones with ketone and halogen. Despite this modification the method still remains cumbersome and time consuming (24-25 hr reflux). Herein, we report a simple procedure for the formation of thiazole, pyrazole and furan rings at a time at the 3rd position of coumarin.

In continuation of our earlier work, on the synthesis of heterocyclic systems derived from coumarin we report herein a multi component reaction that involves the Hantzsch thiazole synthesis and a new synthetic route for the preparation of 3-[2-(3-methyl-4,5-dihydro-furo[2,3-c]-pyrazol-1-yl)-thiazol-4-yl]-chromen-2-ones in one step.

The synthesis of 3-[2-(3-methyl-4,5-dihydro-furo[2,3-c]pyrazol-1-yl)-thiazol-4-yl]-chromen-2-ones has not been reported at 3rd position of coumarin in the literature. Hence, a convenient procedure for the synthesis of the title compounds is described through anhydrous zinc chloride catalyzed one pot condensation of 3-(2-bromoacetyl)coumarin, thiosemicarbazide and 2-acetyl butyrolactone in good yields (82-90%).

In the Method I, condensation of 3-(2-bromoacetyl)coumarin, thiosemicarbazide and α-acetylbutyrolactone in toluene in presence of anhy. ZnCl₂ at refluxing temperature gave crystalline solid 4a. The same compounds were also obtained when reaction is carried out in acetic acid under reflux. The yields of the products 4a-f are good (82-90%, Method I). It is a one step synthesis.

The yields of 4a-f are excellent in Method I using ZnCl₂ in toluene when compared with acetic acid. The reactions are fairly general, rapid, facile and efficient and devoid of any side products. The experimental procedures are very simple.

Compound 4a-f can also be synthesized by an alternative method involving condensation of 3-(2-bromoacetyl)-chromen-2-one with 3-methyl-4,5-dihydrofuro[2,3-c]pyrazol-1-carbothioic acid amide in anhydrous ethanol via Hantzsch thiazole synthesis to yield corresponding 3-[2-(3-methyl-4,5-dihydrofuro[2,3-c]pyrazol-1-yl)thiazol-4-yl]-chromen-2-ones in 70-75% (Method II). The compound 4 can also be synthesized by cyclo condensation of 3-{2-[5-hydroxy-4-(2-hydroxy ethyl)-3-methyl pyrazol-1-yl]thiazol-4-yl}chromen-2-one (ref. 6) in acetic acid. The products obtained by both methods (Methods I and II) were found to be identical by their mixed m.p. measurements, co-TLC and IR spectra.

In order to study the scope of this reaction, six different substituted 3-[2-(3-methyl-4,5-dihydro-furo[2,3-c]pyrazol-1-yl)-thiazol-4-yl]-chromen-2-ones were synthesized. The synthetic strategy permits the introduction of a diverse array of substituents on to the benzene ring. To the best of our knowledge, this is the first report of its kind to construct three rings like...
thiazole, pyrazole and furan in a single step at 3\textsuperscript{rd} position of coumarin. The characterization data for some representative compounds 4\textit{a-f} has been given (Table I). The structures of newly prepared compounds 4\textit{a-f} were confirmed on the basis of IR, \textsuperscript{1}H NMR and mass spectra.

\textbf{Experimental Section}
All melting points were recorded on a Cintex melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 337 spectrophotometer. \textsuperscript{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal
standard (chemical shifts in $\delta$, ppm); and mass spectra on a Jeol-JMS-D mass spectrometer at 70 eV.

The various derivatives of 3-(2-bromoacetyl)coumarins were prepared according to literature method$^{14}$. Representative methods of preparation of compounds $4$, $5$ and $6$ are described below.

**General procedure for the synthesis of 3-[2-(3-methyl-4,5-dihydro-furo[2,3-c]pyrazol-1-yl)-thiazol-4-yl]-chromen-2-one 4a**

**Method Ia**: A mixture of 3-(2-bromoacetyl)chromen-2-one (1.33 g, 5 mmoles), thiosemicarbazide (0.455 g, 5 mmoles) and 2-acetyl butyrolactone (0.53 mL, 5 mmoles) was taken in 20 mL of toluene and treated with anhydrous ZnCl$_2$ (0.30 to 0.5 g) and the reaction-mixture was refluxed for 1 hr, cooled, neutralized by 5% aq. NaHCO$_3$ solution and extracted with ether (4 × 25 mL). The ether extract was washed with water until the washing were neutral to pH = 7, which was then dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuum. The solid thus obtained was recrystallized from methanol. All the other compounds $4b-f$ were prepared similarly. Yield: 82-90%.

**Method Ib**: A mixture of 3-(2-bromoacetyl)chromen-2-one (1.33 g, 5 mmoles, ref. 14), thiosemicarbazide (0.455 g, 55 mmoles) and 2-acetylbutyrolactone (0.53 mL, 55 mmoles) was taken in 20 mL of acetic acid and refluxed for 1 hr. The reaction-mixture was cooled to RT and filtered. The solid thus obtained was washed with water, dried and recrystallized from methanol. All the other compounds $4b-f$ were prepared similarly. The yields of the products are 70-75%.

**Typical procedure for the preparation of 4 and 5**

**Method IIa**: A mixture of 3-(2-bromoacetyl)chromen-2-one (1.33 g, 5 mmoles) with 3-methyl-4,5-dihydro-furo[2,3-c]-pyrazole-1-carbothioic acid amide (0.915 g, 5 mmoles) was taken in 20 mL of anhydrous ethanol and refluxed for 1-2 hr. The reaction-mixture was cooled to RT and the solid obtained was filtered, washed with water, dried and crystallized from methanol. All the other compounds 4b-f were prepared similarly.

**Preparation of 4 from 6**

**Method IIb**: 3-{2-[5-hydroxy-4-(2-hydroxyethyl)-3-methyl-pyrazol-1-yl]thiazol-4-yl}chromen-2-one$^{13}$ 6 (1.845 g, 5 mmole) was taken in 20 mL acetic acid and refluxed for 1 hr. The reaction-mixture was cooled to RT and the solid obtained was washed, washed with water, dried and crystallized from methanol.

$$\text{3-[2-(3-Methyl-4,5-dihydro-furo[2,3-c]pyrazol-1-yl]thiazol-4-yl]chromen-2-one 4a}$$

m.p. 235-37°C. IR (KBr): 1731, 1604 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 2.26 (s, 3H, -CH$_3$), 2.54 (t, 2H, $J = 7$ Hz, -CH$_2$-), 4.06 (t, 2H, $J = 7$ Hz, -O-CH$_2$), 7.40-7.50 (m, 2H, C$_6$ & C$_8$ of coumarin), 7.63-7.68 (m, 1H, C$_8$ of coumarin), 7.82 (d, 1H, $J = 6$ Hz, C$_5$ of coumarin), 8.12 (s, 1H, C$_5$ of thiazole) and 8.80 (s, 1H, C$_4$ of coumarin); EI-MS:

<table>
<thead>
<tr>
<th>Compd*</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Yield (%)</th>
<th>Mol. formula (M.wt)</th>
<th>m.p. (°C)</th>
</tr>
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<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>H</td>
<td>90</td>
<td>C$<em>{18}$H$</em>{13}$N$_3$O$_3$S (351)</td>
<td>235-37</td>
</tr>
<tr>
<td>4b</td>
<td>H</td>
<td>OCH$_3$</td>
<td>88</td>
<td>C$<em>{18}$H$</em>{15}$N$_3$O$_4$S (381)</td>
<td>203-06</td>
</tr>
<tr>
<td>4c</td>
<td>Cl</td>
<td>H</td>
<td>86</td>
<td>C$<em>{18}$H$</em>{12}$N$_3$O$_3$SCl (385.5)</td>
<td>196-98</td>
</tr>
<tr>
<td>4d</td>
<td>Cl</td>
<td>Cl</td>
<td>85</td>
<td>C$<em>{18}$H$</em>{12}$N$_3$O$_3$SCl$_2$ (420)</td>
<td>183-85</td>
</tr>
<tr>
<td>4e</td>
<td>Br</td>
<td>H</td>
<td>84</td>
<td>C$<em>{18}$H$</em>{12}$N$_3$O$_3$SBr (430)</td>
<td>186-88</td>
</tr>
<tr>
<td>4f</td>
<td>Br</td>
<td>Br</td>
<td>82</td>
<td>C$<em>{18}$H$</em>{11}$N$_3$O$_3$SBr$_2$ (509)</td>
<td>188-200</td>
</tr>
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</table>

*The compounds 4a-f were recrystallized from methanol and all the compounds gave satisfactory C, H and N analyses.

<table>
<thead>
<tr>
<th>Compd*</th>
<th>Yield (%)</th>
<th>Mol. formula (M.wt)</th>
<th>m.p. (°C)</th>
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<td>4a</td>
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<td>C$<em>{18}$H$</em>{13}$N$_3$O$_3$S (351)</td>
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<tr>
<td>4b</td>
<td>75</td>
<td>C$<em>{18}$H$</em>{15}$N$_3$O$_4$S (381)</td>
<td>203-06</td>
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<tr>
<td>4c</td>
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<td>196-98</td>
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<tr>
<td>4d</td>
<td>71</td>
<td>C$<em>{18}$H$</em>{12}$N$_3$O$_3$SCl$_2$ (420)</td>
<td>183-85</td>
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<tr>
<td>4e</td>
<td>76</td>
<td>C$<em>{18}$H$</em>{12}$N$_3$O$_3$SBr (430)</td>
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</tr>
<tr>
<td>4f</td>
<td>74</td>
<td>C$<em>{18}$H$</em>{11}$N$_3$O$_3$SBr$_2$ (509)</td>
<td>188-200</td>
</tr>
</tbody>
</table>
351 (M+, 100%). Anal. Calcd. For C₁₈H₁₃N₃O₃S: C, 60.53; H, 3.73; N, 11.96; S, 9.12. Found: C, 60.50; H, 3.70; N, 11.93; S, 9.10%.

8-Methoxy-3-[2-(3-methyl-4,5-dihydro-furo[2,3-c]-pyrazol-1-yl)thiazol-4-yl]chromen-2-one 4b
m.p. 204-206°C. IR (KBr): 1736, 1606, 1542 cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.28 (s, 3H, -CH₃), 2.60 (t, 2H, J = 6 Hz, -CH₂), 3.40 (s, 3H, -OCH₃), 3.90 (t, 2H, J = 7 Hz, -OCH₂₂), 7.70 - 7.80 (m, 1H, Ar-H), 7.82 - 7.98 (m, 2H, Ar-H), 8.10 (s, 1H, C₅ of thiazole) and 8.78 (s, 1H, C₄ of coumarin). Anal. Calcd. For C₁₈H₁₂N₃O₃SBr: C, 50.25; H, 2.81; N, 9.79; S, 7.45. Found: C, 42.46; H, 2.18; S, 8.25; S, 6.30.

3-Methyl-4,5-dihydro-furo[2,3-c]pyrazole-1-carboxylic acid amide 5
m.p. 183-85°C. IR (KBr): 3340, 1608, 1526 cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.20 (s, 3H, -CH₃), 2.40 (t, 2H, J = 6 Hz, -CH₂₂), 3.0 (t, 2H, J = 7.5 Hz, -OCH₂₂) and 9.2 (s, 2H, NH₂, D₂O exchangeable). EIMS (m/z): 183 (M⁺). Anal. Calcd. For C₁₇H₉N₃OS: C, 45.90; H, 4.90; N, 22.95; S, 17.48. Found: C, 45.86; H, 4.89; N, 22.91; S, 17.45%.

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References