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Note

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 **4a-f** 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 **4a-f** 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[1]. Various simple and 3-substituted coumarins have been isolated[2] from natural sources. Coumarins bearing a heterocyclic moiety at 3rd position are uricosuric[3] and CNS active agents[4], further thiazoles[5] and also coumarin derivatives with a heterocyclic system at 3rd position exhibit promising biological activities[6]. A literature survey revealed that thiazoles are generally prepared by Hantzsch thiazole synthesis from α-halo ketones and thioureas and thioamides[7].

Later King *et al*[8,9] and other workers[10] 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[11,12] on the synthesis of heterocyclic systems derived from coumarin[13] 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.

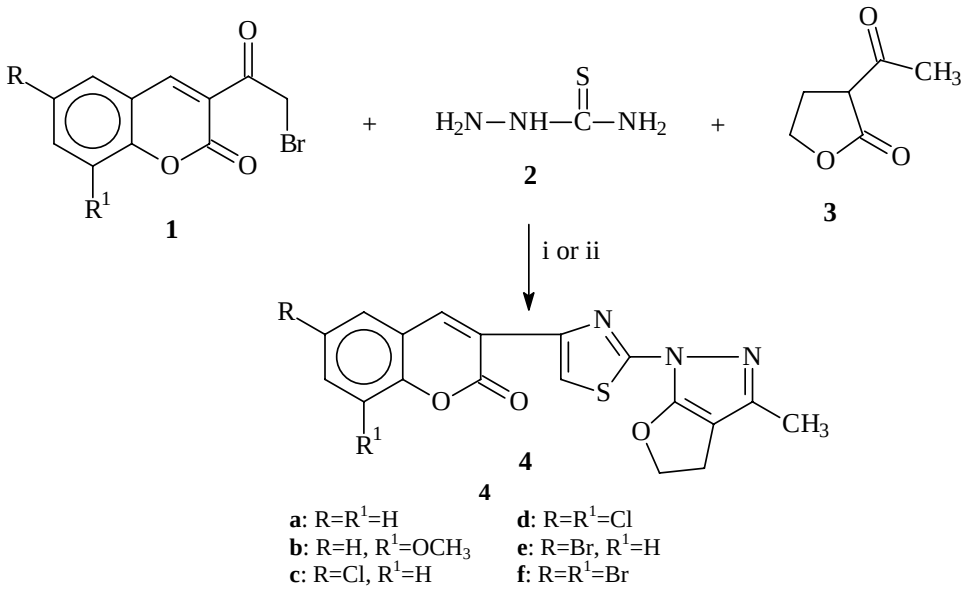
The synthesis of 3-[2-(3-methyl-4,5-dihydro-furo-[2,3-*c*]pyrazol-1-yl)-thiazol-4-yl]-chromen-2-ones has not been reported at 3rd position of coumarin in the literature. Hence, a convenient procedure for the synthesis of the title compounds is described through anhydrous zinc chloride catalyzed one pot 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[14], thiosemicarbazide and α-acetyl-butyrolactone in toluene in presence of anhy. $ZnCl_2$ at refluxing temperature gave crystalline solid **4a**. The same compounds **4a-f** 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 $ZnCl_2$ 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.

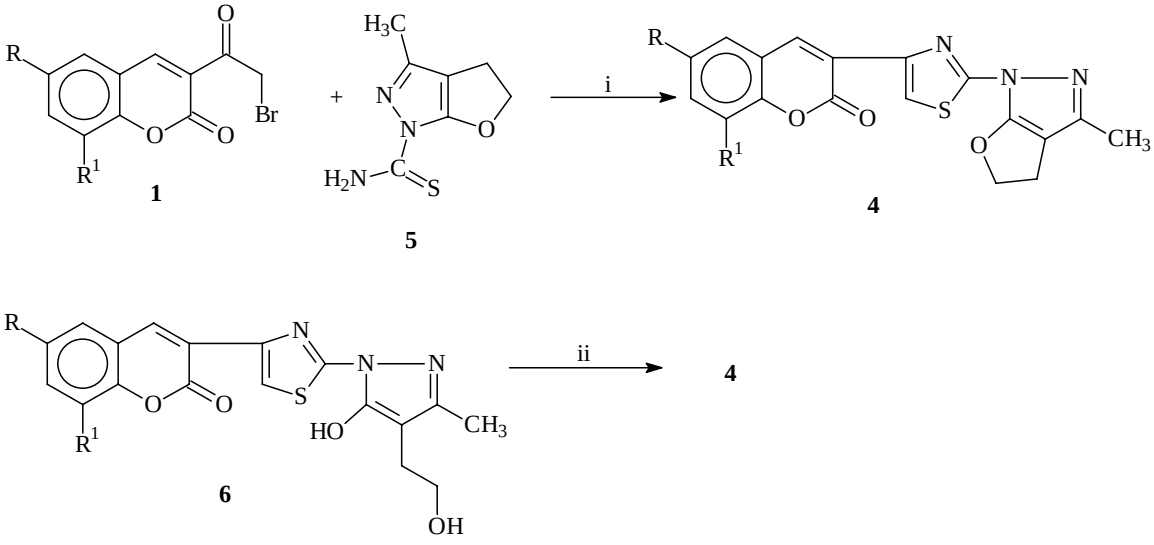
Compound **4a-f** can also be synthesized by an alternative method involving condensation of 3-(2-bromoacetyl)-chromen-2-one **1** with 3-methyl-4,5-dihydrofuro[2,3-*c*]pyrazol-1-carbothioic acid amide **5** in anhydrous ethanol *via* Hantzsch thiazole synthesis to yield corresponding 3-[2-(3-methyl-4,5-dihydro-furo[2,3-*c*]pyrazol-1-yl)thiazol-4-yl]-chromen-2-ones **4** 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 (**Schemes I** and **II**) 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



Reagents and Conditions: i) Anhy. $ZnCl_2$/Toluene, 2 hr, reflux; ii) CH_3COOH/1 hr, reflux

Scheme I — One pot synthesis, method I



Reaction conditions: i) Anhy.C_2H_5OH, 1 hr, reflux; i) CH_3COOH/1 hr, reflux

Scheme II — Alternative synthesis, method II

thiazole, pyrazole and furan in a single step at 3rd position of coumarin. The characterization data for some representative compounds **4a-f** has been given (**Table I**). The structures of newly prepared compounds **4a-f** were confirmed on the basis of IR, ^{1}H NMR and mass spectra.

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. ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal

Table I — Physical characterization data of compounds **4a-f**

Compd*	R R^1	Yield (%) Method I	 Method II	Mol.formula (M.wt)	m.p. (°C)
4a	H H	90	75	$C_{18}H_{13}N_3O_3S$ (351)	235-37
4b	H OCH_3	88	73	$C_{19}H_{15}N_3O_4S$ (381)	203-06
4c	Cl H	86	71	$C_{18}H_{12}N_3O_3SCl$ (385.5)	196-98
4d	Cl Cl	85	70	$C_{18}H_{11}N_3O_3SCl_2$ (420)	183-85
4e	Br H	84	76	$C_{18}H_{12}N_3O_3SBr$ (430)	186-88
4f	Br Br	82	74	$C_{18}H_{11}N_3O_3SBr_2$ (509)	188-200

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

standard (chemical shifts in δ, 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 *p*H = 7, which was then dried over anhydrous Na_2SO_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%.

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 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 filtered. The solid thus obtained was 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 filtered, washed with water, dried and crystallized from methanol.

3-[2-(3-Methyl-4,5-dihydro-furo[2,3-*c*]pyrazol-1-yl)thioazol-4-yl]chromen-2-one 4a. m.p. 235-37°C. IR (KBr): 1731, 1604 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.26 (s, 3H, $-CH_3$), 2.54 (t, 2H, *J* = 7Hz, $-CH_2-$), 4.06 (t, 2H, *J* = 7Hz, $-O-CH_2$), 7.40-7.50 (m, 2H, C_6 & C_8 of coumarin), 7.63-7.68 (m, 1H, C_7 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:

351 (M^+, 100%). Anal. Calcd. For $C_{18}H_{13}N_3O_3S$: 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-d_6): δ 2.28 (s, 3H, -CH_3), 2.60 (t, 2H, J = 6 Hz, -CH_2), 3.40 (s, 3H, -OCH_3), 3.90 (t, 2H, J = 7 Hz, -OCH_2-), 7.70 - 7.80 (m, 1H, Ar-H), 7.82 – 7.98 (m, 2H, Ar-H), 8.10 (s, 1H, C_5 of thiazole) and 8.78 (s, 1H, C_4 of coumarin). Anal. Calcd. For $C_{19}H_{15}N_3O_4S$: C, 59.84; H, 3.96; N, 11.03; S, 8.44. Found: C, 59.81; H, 3.93; N, 11.00; S, 8.40%.

6-Chloro-3-[2-(3-methyl-4,5-dihydro-furo[2,3-*c*]py-razol-1-yl)thiazol-4-yl]chromen-2-one 4c

m.p. 196-98°C. IR (KBr): 1736, 1604, 1554 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.26 (s, 3H, -CH_3), 2.60 (t, 2H, J = 6 Hz, -CH_2-), 3.80 (t, 2H, J = 7 Hz, -OCH_2-), 7.60 – 7.70 (m, 3H, Ar-H), 8.20 (s, 1H, C_5 of thiazole) and 8.80 (s, 1H, C_4 of coumarin). Anal. Calcd. For $C_{18}H_{12}N_3O_3SCl$: C, 56.03; H, 3.13; N, 10.89; S, 8.31. Found: C, 56.00; H, 3.10; N, 10.85; S, 8.28%.

6,8-Dichloro-3-[2-(3-methyl-4,5-dihydro-furo[2,3-*c*]-pyrazol-1-yl)-thiazol-4-yl]chromen-2-one 4d

m.p. 183-85°C. IR (KBr): 1731, 1603, 1540 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H, -CH_3), 2.5 (t, 2H, J = 7 Hz, -CH_2-), 3.65 (t, 2H, J = 7 Hz, -O-CH_2-), 7.10-7.30 (m, 3H, Ar-H), 8.14 (s, 1H, C_5 of thiazole) and 8.80 (s, 1H, C_4 of coumarin). Anal. Calcd. For $C_{18}H_{11}N_3O_3SCl_2$: C, 51.44; H, 2.64; N, 10.00; S, 7.63. Found: C, 51.40; H, 2.60; N, 9.98; S, 7.60%.

6-Bromo-3-[2-(3-methyl-4,5-dihydro-furo[2,3-*c*]py-razol-1-yl)-thiazol-4-yl]-chromen-2-one 4e

m.p. 186-88°C. IR (KBr): 1731, 1600, 1540 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, -CH_3), 2.50 (t, 2H, J = 6 Hz, -CH_2-), 3.70 (t, 2H, J = 7 Hz, -O-CH_2-), 7.20 – 7.35 (m, 2H, C_7 and C_8 of coumarin), 7.60-7.70 (m, 1H, C_5 of coumarin), 8.10 (s, 1H, C_5 of thiazole) and 8.75 (s, 1H, C_4 of coumarin). Anal. Calcd. For $C_{18}H_{12}N_3O_3SBr$: C, 50.25; H, 2.81; N, 9.79; S, 7.45. Found: C, 50.21; H, 2.78; N, 9.74; S, 7.41%.

6,8-Dibromo-3-[2-(3-methyl-4,5-dihydro-furo[2,3-*c*]pyrazol-1-yl)thiazol-4-yl]-chromen-2-one 4f

m.p. 188-200°C. IR (KBr): 1716, 1606, 1551 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.28 (s, 3H, -CH_3), 2.39 (t, 2H, J = 6 Hz, -CH_2-), 3.99 (t, 2H, J = 7 Hz, -O-CH_2-), 7.40 – 7.51 (m, 3H, Ar-H), 8.12 (s, 1H, C_5 of thiazole) and 8.98 (s, 1H, C_4 of coumarin). Anal. Calcd. For $C_{18}H_{11}N_3O_3SBr_2$: C, 42.46; H, 2.18; N, 8.25; S, 6.30. Found: C, 42.43; H, 2.14; N, 8.21; S, 6.27%.

3-Methyl-4,5-dihydro-furo[2,3-*c*]pyrazole-1-carbo-thioic acid amide 5

m.p. 183-85°C. IR (KBr): 3340, 1608, 1526 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (s, 3H, -CH_3), 2.40 (t, 2H, J = 6 Hz, -CH_2-), 3.0 (t, 2H, J = 7.5 Hz, -O-CH_2-) and 9.2 (s, 2H, NH_2, D_2O exchangeable). EIMS (*m/z*): 183 (M^+). Anal. Calcd. For $C_7H_9N_3OS$: 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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