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# Facile One-Pot Synthesis of 3-{2-[5-Hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-ones via a Three-Component Reaction

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**Abstract:** Reaction of 3-(2-bromo-acetyl)-chromen-2-one with thiosemicarbazide and 2-acetylbutyro lactone in anhydrous ethanol gave 3-{2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one in good yields.

**Keywords:** 2-Acetylbutyrolactone, benzopyran-2-one, pyrazoles, thiazoles

A number of natural products and synthetic analogs of the coumarin structural moiety display wide-ranging biological properties.[1,2] Coumarins bearing a heterocyclic moiety at the third position are spasmolytic, uricosuric,[3] and CNS active agents,[4] further thiazoles,[5] and also coumarin derivatives with a heterocyclic system at the third position all exhibit promising biological activities.[6] A literature survey revealed that thiazoles are generally prepared by Hantzsch thiazole synthesis from $\alpha$-halogenoketones, thioureas, and thioamides.[7] Later King et al.[8,9] and other workers[10] synthesized amino thiazoles by replacing $\alpha$-halogenoketones with ketone and halogen. Despite this modification, the method still remains cumbersome and time consuming[11] (24–25 h reflux).

In continuation of our earlier work on the synthesis of heterocyclic systems derived from coumarin,[12,13] we report herein a multicomponent

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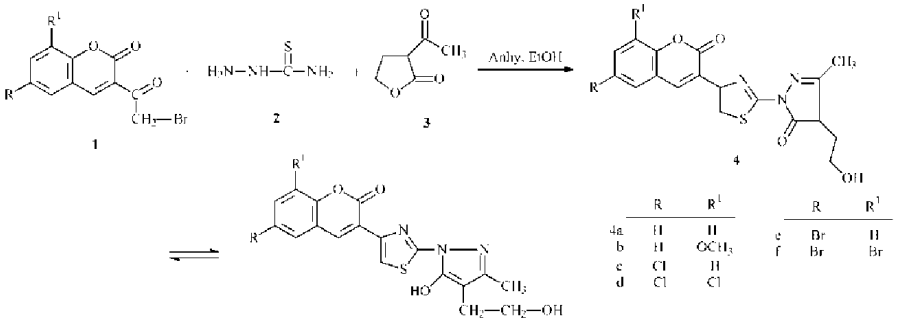


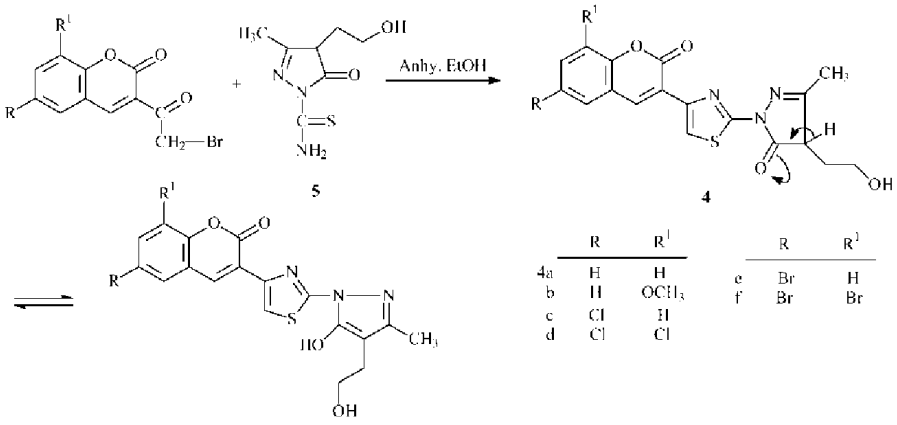

***Scheme 1.*** Method 1.

reaction that involves the Hantzsch thiazole synthesis and formation of a pyrazole skeleton (Scheme 1).

In the one-step synthesis, 3-(2-bromo-acetyl)-chromen-2-one (1.33 g, 5 mmol), thiosemicarbazide (0.455 g, 5 mmol), and 2-acetylbutyrolactone (0.53 ml, 5 mmol) in anhydrous ethanol gave 3-{2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]thiazol-4-yl}-chromen-2-one.

Compound 4 can also be synthesized by an alternative method involving condensation of 3-(2-bromo-acetyl)-chromen-2-one with 5-hydroxy-4-(2-hydroxy-ethyl)-3-methylpyrazol-1-carbothioic acid amide in ahydrous ethanol to yield the corresponding 3-{2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one in 70–75%. The products obtained by both the methods were found to be identical (Scheme 2).

In all the cases, the compound **4** existed in enolic structures except **4b**. The enolic structure for the compound **4** was indicated by the absence of an IR absorption due to the ring C═O and the presence of a strong absorption due to the —OH functional group in the region 3212–3279 $cm^{-1}$. This




***Scheme 2.*** Method 2.

was further confirmed by the PMR spectrum in which signals at $\delta$ 12 ppm integrating for one proton were attributed and intramolecular hydrogen bonded OH. The versatility of the approach was illustrated by the synthesis of **4a**–**4f**.

## EXPERIMENTAL

Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and are uncorrected. The purity of the compounds was checked by TLC plates. IR spectra were recorded in KBr disks on a Bruker WM-400 spectrometer. $^1$H NMR spectra were recorded on a Bruker WM-300 spectrometer (in $\delta$ ppm) using TMS as internal standard. Mass spectra (EI-MS) were determined on Jeol-D-300 spectrometer at 70 eV. The 3-(2-bromoacetyl)-chromen-2-ones (**1**) were prepared by reported procedures.[11]

### General Procedure for the Synthesis of 3-{2-[5-Hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one (4a–f)

A mixture of 3-(2-bromoacetyl)-chromen-2-one (1.33 g, 5 mmol) with thiosemicarbazide (0.455 g, 5 mmol) and 2-acetylbutyrolactone (0.53 ml, 5 mmol) in 20 ml of anhydrous ethanol was refluxed for 30 min. The reaction mixture was cooled to room temperature and filtered. The solid thus obtained was washed with water, dried, and recrystallized from methanol. All the other compounds **4b**–**4f** were prepared similarly.

### Data

**3-{2-[5-Hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one (4a):** Recrystallized from methanol. Yield 90% (1.66 g), mp 210–212°C. IR (KBr), $\nu$ 1604 (—C═N), 1691 (lactone —C═O), 3242–3479 (—OH). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.25 (s, 3H, $CH_3$), 2.39 (t, 2H, —$CH_2$), 2.51 (s, 1H, OH, $D_2O$ exchangeable), 3.47 (t, 2H, —$CH_2O$—), 7.14–7.48 (m, 2H, $C_6$ & $C_8$ of coumarin), 7.62–7.67 (m, 1H, $C_7$ of coumarin), 7.82 (d, 1H, $J = 6$ Hz $C_5$ of coumarin), 8.10 (s, 1H, $C_5$ of thiazol) and 8.79 (s, 1H, $C_4$ of coumarin), and 12.00 (s, 1H, enolic OH, $D_2O$ exchangeable). Anal. calcd. for $C_{18}H_{15}N_3O_4S$: C, 58.53; H, 4.09; N, 11.38; S, 8.68. Found: C, 58.50; H, 4.06; N, 11.34; S, 8.64.

**3-{2-[5-Hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-8-methoxy-chromen-2-one (4b):** Recrystallized from methanol. Yield 86%

(1.71 g), mp 178–180°C. IR (KBr), $\nu$ 1578 (C═C), 1608 (—C═N), 1642 (—C═O), 1702 (lactone —C═O), 3365 (—OH). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.29 (s, 3H, $CH_3$), 2.39 (t, 2H, —$CH_2$), 2.51 (s, 1H, aliphatic —OH), 3.49 (m, 3H, 2H of —$CH_2$—O— and 1H of pyrazolone), 3.95 (s, 3H, —$OCH_3$), 7.35–7.40 (m, 3H, Ar-H), 8.14 (s, 1H, $C_5$-H of thiazol), 8.75 (s, 1H, $C_4$ of coumarin), and 11.92 (s, 1H, OH). Anal. calcd. for $C_{19}H_{17}N_3O_5S$: C, 57.13; H, 4.29; N, 10.52; S, 8.03. Found: C, 57.10; H, 4.24; N, 10.48; S, 8.00.

**6-Chloro-3-{2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one (4c):** Recrystallized from methanol. Yield 80% (1.61 g), mp 188–190°C. IR (KBr), $\nu$ 1605 (—C═N), 1728 (lactone —C═O), 3412 (—OH). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.24 (s, 3H, —$CH_3$), 2.36 (t, 2H, —$CH_2$), 3.49–3.95 (m, 3H, —$CH_2$—O— and —OH, $D_2O$ exchangeable), 7.33–7.78 (m, 3H, Ar-H), 8.14 (s, 1H, $C_5$ of thiazol), 8.83 (s, 1H, $C_4$ of coumarin), and 11.66 (s, 1H, —OH of pyrazol, $D_2O$ exchangeable). Anal. calcd. for $C_{18}H_{14}N_3O_4SCl$: C, 53.54; H, 3.49; N, 10.40; S, 7.94. Found: C, 53.50; H, 3.46; N, 10.35; S, 7.90.

**6,8-Dichloro-3-{2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one (4d):** Recrystallized from methanol. Yield 85% (1.85 g), mp 175–177°C. IR (KBr), $\nu$ 1531 (—C═C—), 1607 (—C═N), 1728 (lactone —C═O), 3420 (—OH). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.24 (s, 3H, $CH_3$), 2.38 (t, 2H, —$CH_2$), 2.84 (s, 1H, aliphatic OH, $D_2O$ exchangeable), 3.48 (t, 2H, —$CH_2$—O—), 7.15 (d, 1H, Ar-H, $J = 3$ Hz), 7.76 (d, 1H, Ar-H, J = 3 Hz), 8.14 (s, 1H, $C_5$ of thiazol), 8.72 (s, 1H, $C_4$ of coumarin), and 11.85 (s, 1H, —OH, $D_2O$ exchangeable). Anal. calcd. for $C_{18}H_{13}N_3O_4SCl_2$: C, 49.33; H, 2.99; N, 9.59, S, 7.32. Found: C, 49.30; H, 2.95; N, 9.54; S, 7.25.

**6-Bromo-3-{2-[5-Hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one (4e):** Recrystallized from methanol. Yield 84% (1.88 g), mp 204–206°C. IR (KBr), $\nu$ 1612 (—C═N), 1723 (lactone —C═O), 3397 (—OH). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.23 (s, 3H, —$CH_3$), 2.39 (t, 2H, —$CH_2$), 4.10 (s, 1H, aliphatic —OH, $D_2O$ exchangeable), 3.49 (t, 2H, —$CH_2$—O—), 7.48 (d, 1H, $J = 7$ Hz, $C_8$ of coumarin), 7.82 (d, 1H, $J = 8$ Hz, $C_7$ of coumarin), 8.07 (d, 1H, $J = 2$ Hz, $C_5$ of coumarin), 8.14 (s, 1H, $C_5$ of thiazol), 8.71 (s, 1H, $C_4$ of coumarin), and 11.9 (s, 1H, OH, $D_2O$ exchangeable). Anal. calcd. for $C_{18}H_{14}N_3O_4SBr$: C, 48.23; H, 3.15; N, 9.37; S, 7.15. Found: C, 48.20; H, 3.11; N, 9.33; S, 7.11.

**6,8-Dibromo-3-{2-[5-hydroxy-4-(2-hydroxy-ethyl)-3-methyl-pyrazol-1-yl]-thiazol-4-yl}-chromen-2-one (4f):** Recrystallized from methanol. Yield 82% (2.16 g), mp 195–197°C. IR (KBr), $\nu$ 1535 (—C═C—), 1620 (C═N), 1738 (lactone —C═O), 3402 (—OH). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.24 (s, 3H,

—$CH_3$), 2.39 (t, 2H, —$CH_2$), 3.39–3.52 (m, 1H of OH, $D_2O$ exchangeable and 2H of —$CH_2$—O—), 8.11–8.15 (m, 3H, 2H, Ar-H of coumarin and 1H of thiazol), 8.71 (s, 1H, $C_4$ of coumarin) and 11.83 (s, 1H, OH of pyrazol, $D_2O$ exchangeable). Anal. calcd. for $C_{18}H_{13}N_3O_4SBr_2$: C, 41.01; H, 2.49; N, 7.97; S, 6.08. Found: C, 41.00; H, 2.44; N, 7.92; S, 6.00.

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