Synthesis of some 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H[1,3]thiazolo[3,2-a]-pyrimidin-5-ones

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Received 12 September 2007; accepted (revised) 25 February 2008

Reaction of 3-(2-amino-4-thiazolyl)coumarins with ethyl acetoacetate in a mixture of PPA and POCl₃ give 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-thiazolo[3,2-a]pyrimidin-5-ones in a single step. Alternatively condensation of 3-(2-amino-4-thiazolyl)coumarins with acetoacetic ester (EAA) results in the formation of Schiff bases. These on further reaction with polyphosphoric acid (PPA) and phosphorus oxychloride (POCl₃) give corresponding cyclised compounds. 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H[1,3]thiazolo[3,2-a]pyrimidin-5-ones. The structures of newly prepared compounds have been confirmed from analytical and spectral data.

Keywords: Benzopyran-2-one, pyrimidin-5-ones, thiazoles, thiazolo pyrimidones

Coumarins constitute an important class of naturally occurring oxygen ring compounds. The chemistry of Coumarin derivatives continues to draw attention of synthetic organic chemists due to their varied biological activities. Further thiazoles and coumarin derivatives with heterocyclic system at 3rd position exhibit promising biological activities. A literature survey revealed that thiazoles are generally prepared by Hantzsch thiazole synthesis from α-haloketones and thioureas and thioamides. Later King et al. and other workers synthesized amino thiazoles by replacing α-haloketones with ketone and halogen. Despite this modification the method still remains cumbersome and time-consuming (24-25 hr reflux).

In continuation of earlier work on the synthesis of heterocyclic systems derived from coumarin, synthesis of heterocyclic thiazolo pyrimidine-5-ones derived from coumarins is reported. Cyclocondensation reaction of 3-(2-amino-4-thiazolyl)coumarin with ethyl acetoacetate in a mixture of POCl₃ + PPA gave 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H[1,3]thiazolo[3,2-a]pyrimidin-5-ones (Scheme I). This is a one step process.

Ring closure of the ester does not proceed in POCl₃ or PPA alone and similar is true in the one pot synthesis of title compounds 4a-g. Maximum yields of 4a-g can be achieved, however, by adding some what more than a catalytic amount of PPA to the mixture containing reactants and POCl₃. POCl₃ acts both as a solvent and as an alcohol or water scavenger, rendering cyclization irreversible, but its presence is also advantageous during workup. The mixed reagent has already been used for the preparation of several nitrogen bridgehead systems but its scope has not been studied in detail. The present article describes the importance of mixed reagent in the preparation of the title bridgehead system. The yields are maximum in one step process (70-85%).

Reaction of 3-(2-bromoacetyl) coumarins with thiourea resulted in the formation of 3-(2-amino-4-thiazolyl) coumarins, condensation of these compounds with ethyl acetoacetate (EAA) gave the corresponding schiff bases. These on cyclization with a mixture of PPA+POCl₃ gave the 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H[1,3]thiazolo[3,2-a]pyrimidin-5-ones (Scheme II). This is a two step process (yield 60-70%, Table I).

The characterization data for some representative compounds 3a-f and 4a-f has been given. The IR spectra of compounds 3a showed prominent peaks 1615 (-C=N), 1651 (-COO) and 1716 cm⁻¹ (lactone, -C=O) consistent with the assigned structures. The ¹H NMR spectrum of 3a showed a characteristic triplet for CH₃ at δ 1.31 and singlet for –N=C-CH₃ at 2.48, quartet for –CH₂₃ of ethyl at 4.25, at 4.89 for –CH₂ of side chain. The coumarin C⁴ proton appeared as singlet at δ 8.54. The remaining protons were observed in the usual region.
The IR spectra of compounds 4a showed prominent peaks at 1684 (-C=O, pyrimidine) and 1720 cm⁻¹ (lactone, -C=O). The ¹H NMR spectrum of 4a showed characteristic singlet for –CH₃ at δ 6.07 and coumarin C₄ proton appeared as singlet at 8.13. The remaining protons were observed in the usual region.

**Experimental Section**

All melting points were determined in open capillaries with a cintex melting point apparatus. The purity of the compounds was checked by TLC plates. IR spectra were recorded on a Perkin-Elmer model 337 IR spectrophotometer. ¹H NMR (300 MHz)
spectra were recorded on a Varian DPX 300 instrument in CDCl$_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in $\delta$ ppm. Mass spectra (EI-MS) were determined on a Jeol-D-300 spectrometer at 70 eV. The 3-(2-bromoacetyl)-chromen-2-ones I were prepared by reported procedures.$^{12}$

Preparation of 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]-pyrimidin-5-one 4a
A mixture of 3-(2-amino-4-thiazolyl)-2H-1-benzopyran-2-one (0.01 mole) and ethylacetoacetate (0.01 mole) was suspended in POCl$_3$ (0.03 mole) at RT. Then to the reaction-mixture freshly prepared polyphosphoric acid (0.003 mole) was added. The temperature of the mixture was raised to 90°C and 25 mL of H$_2$O was added. Filtered the solid, washed with 5% aqueous NaHCO$_3$ solution and recrystallized from methanol.

Preparation of 3-[4-(2-oxo-2H-chromen-3-yl)-thiazol-2-ylimino]-butyric acid ethyl ester 3a.
A mixture of 3-(2-amino-4-thiazolyl) coumarin (0.244 g, 1mmole) and ethylacetoacetate (5 mL) was taken. The reaction-mixture was refluxed in an oil bath for about 4 hr, at 140°C, then the mixture was cooled at RT, the solid separated was filtered, dried and recrystallized from methanol. All the other compounds 3b-g were prepared similarly.

Table I — Preparation of 7-methyl-3-(2-oxo-2H-chromen-3-yl)-thiazolo[3,2-a]-pyrimidin-5-ones and its derivatives and preparation of 3-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-ylimino]butyric acid ethyl ester 3a

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m.p. 198°C; IR (KBr): 1540 (C=C), 1604 (-C=N), 1659 (-COO, ester), 1727 (lactone, -C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 1.31 (t, 3H, CH₃ of CH₂-CH₃), 2.54 (s, 3H, CH₃ of N-C=O), 4.25 (q, 2H, -CH₂- of ethyl), 4.98 (s, 2H, -CH₂-), 7.40 (d, 1H, C₆-H of coumarin, J = 7 Hz), 7.65 (d, 1H, C₇ of coumarin, J = 8 Hz), 7.98 (d, 1H, C₅ of coumarin, J = 2 Hz), 8.10 (s, 1H, C₄ of thiazole), 8.55 (s, 1H, C₉ of coumarin). Anal. Calcd. for C₁₈H₁₅N₂O₂S: C, 49.67; H, 3.47; N, 6.44; S, 7.89. Found: C, 49.37; H, 2.33; N, 7.20; S, 8.24.

3-[4-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)-thiazol-2-ylimino]-butyric acid ethyl ester 3f. Yellow solid; m.p. 218°C; IR (KBr): 1538 (C=C), 1625 (C=O, ester), 1720 (lactone, -C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 2.50 (s, 3H, -CH₃ of ethyl), 4.99 (s, 2H, -CH₂- of ethyl), 7.35 (d, 1H, Ar-H, J = 7.5 Hz), 7.78 (d, 1H, Ar-H, J = 2Hz), 8.10 (s, 1H, C₅ of thiazole), 8.55 (s, 1H, C₉ of coumarin). Anal. Calcd. for C₁₈H₁₅N₂O₂SBr: C, 49.64; H, 3.44; N, 6.40; S, 7.34%.

Preparation of 7-methyl-3-(2-oxo-2H-chromen-3-yl)-thiazolo[3,2-a]pyrimidin-5-one 4a. A mixture of 3-[4-(2-oxo-2H-chromen-3-yl)-thiazol-2-ylimino]-butyric acid ethyl ester (0.01 mole) and polyphosphoric acid (0.025 mole) was heated to 80°C, then added phosphorus oxychloride (0.05 mole). The reaction-mixture was refluxed for about 2 hr, at 80-85°C. The mixture was cooled at RT and diluted with 20 mL of water. The solid separated was filtered, washed with 5% sodium bicarbonate solution and recrystallised from methanol. All the other compounds 4b-g were prepared similarly.

7-Methyl-3-(2-oxo-2H-chromen-3-yl)-thiazolo[3,2-a]pyrimidin-5-one 4a. Brown solid; m.p. 230°C; IR (KBr): 1600 (C=C), 1684 (C=O, pyrimidine), 1720 (lactone, -C=O) cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.28 (s, 3H, -CH₃), 6.07 (s, 1H, pyrimidine), 7.31-7.79 (m, 5H, Ar-H), 8.13 (s, 1H, C₄ of coumarin). Anal. Calcd. for C₁₆H₁₄N₂O₂S: C, 61.93; H, 3.25; N, 9.03; S, 10.33. Found: C, 61.90; H, 3.22; N, 9.00; S, 10.30%.

3-(6-Chloro-2-oxo-2H-chromen-3-yl)-7-methyl-thiazolo[3,2-a]pyrimidin-5-one 4c. Brown solid; m.p. >300°C; IR (KBr): 1603 (C=C), 1676 (-C=O, pyrimidine), 1724 (lactone, -C=O) cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.28 (s, 3H, -CH₃), 6.08 (s, 1H, pyrimidine), 7.53 (d, 1H, J=8Hz, Ar-H), 7.62 (s, 1H, C₅ of thiazole), 7.69-7.73 (dd, 1H, Ar-H), 7.92 (d, 1H, J=2.4Hz, Ar-H), 8.08 (s, 1H, C₄ of coumarin). Anal. Calcd. for C₁₆H₁₄N₂O₂SCl: C, 55.74; H, 2.63; N, 8.13; S, 9.30. Found: C, 55.70; H, 2.60; N, 8.10; S, 9.26%.

Acknowledgement
The authors are thankful to Head, RSIC, IIT Chennai for analytical and spectral data. Further, the authors thank UGC, New Delhi for the financial support (No, F-12-106/2001, SR-I).

References