An Efficient One Pot Synthesis of 3-(2-oxo-2H-chromen-3-yl)-6*H*,8*H*-Pyrimido[4,5-*c*]Pyridazine-5,7-Diones

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An easy, simple and versatile one step synthesis of 3-(2-oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]-pyridazine-5,7-diones is reported by reaction of 3-acetylcoumarins (**1**) with alloxan monohydrate (**2**) in acetic acid followed by hydrazine hydrate.

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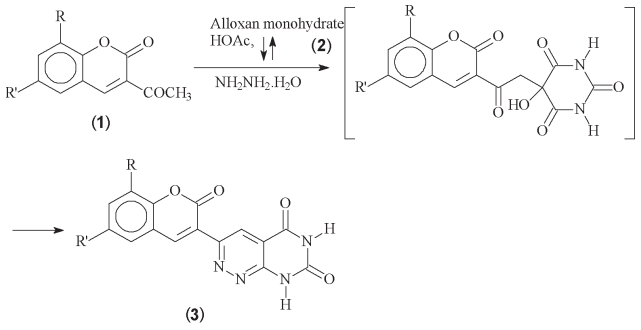
Pyridazines are an important group of heterocyclic compounds, several derivatives of which have been found to possess diverse types of biological activities like diuretic effects [1,2], cytotoxic properties [3,4], topoisomerase inhibitory activities [5]. The coumarin nucleus is found in a variety of natural products, which exhibit various biological effects. Numerous reports have appeared in the literature describing antimicrobial [6], urecosuric and platelet aggregation inhibitory activity [7,8]. Prompted by the above observations and in continuation of our earlier work on coumarins [9,10] we herein report the facile one pot synthesis of 3-(2-oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione (**3**) in a single step from easily available starting materials. Although many good general methods are available [11] for the preparation of pyrimido pyridazines, little has been reported regarding the direct synthesis of these compounds.

Herein, we report a new and direct method for the conversion of 3-coumarinyl α-methylketones to the corresponding pyrimido pyridazinediones (**3**) by use of the reaction of 3-acetylcoumarins [12] with alloxan monohydrate (**2**) and hydrazine hydrate in acetic acid.



The reactions were completed by heating 2-2.5 h and clean in all cases. The steric influence of alloxan monohydrate had no effect on the efficiency of the pyridazine formation. Furthermore the utility of present method was demonstrated by preparing 3-(2-oxo-2*H*-benzo[*h*]-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione (90% yield) and 3-(6,8-dibromo-2-oxo-2*H*-chromen-3-y)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione (83%) in good yields. Probably the reaction of 3-acetylcoumarins with alloxan monhydrate resulted in the formation of intermediate aldol adducts. These on treatment with hydrazine hydrate undergo *in situ* cyclodehydration to give title compounds (**3**). In summary the method described herein provides an excellent approach for the direct transformation of 3-coumarinyl-8*H*-pyrimido[4,5-*c*]pyridazine-5,7-diones. The reactions are fairly general, rapid, facile, efficient and devoid of any side products. The experimental procedures are very simple. We believe that this method will present a better and more practical alternative to the existing methodologies and should find wide spread applications. The application of the present method for the synthesis of other pyrimido-pyridazines with anticancer activity is currently underway.

Table 1

Entry	Compound	R	R'	Yield (%) [a,b]
1	**3a**	H	H	84
2	**3b**	H	Br	89
3	**3c**	Br	Br	83
4	**3d**	H	Cl	88
5	**3e**	Cl	Cl	87
6	**3f**	Cl	NO_2	86
7	**3g**	Benzo[*h*]	---	90

[a] Yield of pure isolated products; all the compounds are recrystallized from dimethyl formamide and methanol; [b] Products are characterized by their physical constants and spectral data.

EXPERIMENTAL

All melting points were determined in open capillary tubes using a sulphuric acid bath and were uncorrected. IR spetra (ν_{max}, cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer. The ^1H NMR spectra were recorded on a Varian 200 MHz unit, and the chemical shifts were recorded in δ (ppm) using TMS as an internal standard. The mass spectra are scanned on Jeol-JMS 300 spectrometer at 70 eV. Elemental analyses were determined and are within ± 0.4% of the calculated values unless otherwise noted.

Typical Experimental Procedure for the Synthesis of 3-(2-Oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione.

A solution of alloxan monohydrate (**2**) (2 mmol) and 3-acetylcoumarin (**1**) (2 mmol) in 4 ml of glacial acetic acid was heated at reflux for 2.5 h. The reaction mixture was allowed to cool to room temperature and then hydrazine hydrate (98%) was added. After stirring overnight, the reaction mixture was filtered and the solution was evaporated to dryness. The resulting residue was treated with ethyl acetate to give the little compound. The compound was recrystallized from a mixture of dimethyl formamide and methanol.

3-(2-Oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione (**3a**) (**entry 1**).

This compound has the following properties: mp = 274-276 °C; IR (KBr, cm^{-1}): 1610, 1681, 1716, 3248; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.14 (s, 1H, pyridazine), 7.26 – 7.31 (m, 2H, H_6 and H_8 of coumarin), 7.60 – 7.70 (m, 2H, H_5 and H_7 of coumarin), 8.51 (s, 1H, C_4 of coumarin), 11.14 (s, 1H, -CONH-CO-) and 12.80 (s, 1H, -NH-CO), mass: m/z 308 (60%), 173 (100%).

Anal. Calcd. for $C_{15}H_8N_4O_4$ (308): C, 58.45; H, 2.62; N, 18.18. Found: C, 58.43; H, 2.60; N, 18.15.

3-(6-Bromo-2-oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]-pyridazine-5,7-dione (**3b**) (**entry 2**).

This compound has the following properties: m.p. 282-284 °C; IR (KBr, cm^{-1}): 1672, 1689, 1730, 3253, 3460; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 6.85 – 7.95 (m, 3H, Ar-H), 8.2 (s, 1H, pyridazine), 8.8 (s, 1H, C_4 of coumarin), 11.10 (s, 1H, CONHCO) and 11.40 (s, 1H, -NHCO-), Mass: mz 387 (M^+).

Anal. Calcd. for $C_{15}H_7N_4BrO_4$ (3.87): C, 46.51; H, 1.80; N, 14.44. Found: C, 46.54; H, 1.82; N, 14.47.

3-(6,8-Dibromo-2-oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione (**3c**) (**entry 3**).

This compound has the following properties: m.p. 248-250 °C; IR (KBr, ν_{max} cm^{-1}): 1675, 1682, 1720, 3245, 3455; ^{1}HNMR (DMSO-d_6): δ 7.75 (d, 1H, C_7, Ar-H, J=2Hz), 8.0 (d, 1H, J=2Hz, C_5 Ar-H), 8.3 (s, 1H, pyridazine), 8.70 (s, 1H, C_4 of coumarin), 11.20 (s, 1H, CONHCO) and 11.50 (s, 1H, NHCO-).

Anal. Calcd. for $C_{15}H_6N_4O_4Br_2$ (466): C, 38.62; H, 1.30; N, 12.02. Found: C, 38.60; H, 1.27; N, 12.00.

3-(6-Chloro-2-oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione (**3d**) (**entry 4**).

This compound has the following properties: m.p. 279-281 °C; IR (KBr, ν_{max} cm^{-1}): 1665, 1725, 3548, 3470; ^{1}HNMR (DMSO-d_6): δ 7.20-7.40 (m, 3H, Ar-H), 8.3 (s, 1H, pyridazine), 8.6 (s, 1H, C_4 of coumarin), 11.00 (s, 1H, CONHCO) and 11.50 (s, 1H, NHCO-).

Anal. Calcd. for $C_{15}H_7N_4O_4Cl$ (342.5): C, 52.55; H, 2.04; N, 16.35. Found: C, 52.52; H, 2.00; N, 16.31.

3-(6,8-Dichloro-2-oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]-pyridazine-5,7-dione (**3e**) (**entry 5**).

This compound has the following properties: m.p. 246-248 °C; IR (KBr, ν_{max} cm^{-1}): 1565, 1680, 1685, 1725, 3245; ^{1}HNMR (200 MHz, DMSO-d_6): δ - 7.60 (d, 1H, C_7, Ar-H, J=2Hz), 7.70 (d, 1H,C_5, Ar-H, J=2Hz) 8.40 (s, 1H, pyridazine), 8.80 (s, 1H, C_4 of coumarin), 11.30 (s, 1H, CONHCO) and 11.60 (s, 1H, NHCO-);

Anal. Calcd. for $C_{15}H_7N_4O_4Cl_2$ (378): C, 47.74; H, 1.60; N, 14.86. Found: C, 47.72; H, 1.57; N, 14.83.

3-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-6*H*,8*H*-pyrimido[4,5-*c*]pyridazine-5,7-dione (**3f**) (**entry 6**).

This compound has the following properties: m.p. 222-224 °C; IR (KBr, ν_{max} cm^{-1}): 1560, 1675, 1680, 1720, 3450; ^{1}HNMR (200 MHz, DMSO-d_6): δ - 7.00-7.30 (m, 3H, Ar-H), 8.10 (s, 1H, pyridazine), 8.60 (s, 1H, C_4 of coumarin), 11.20 (s, 1H, CONHCO) and 11.60 (s, 1H, NHCO-).

Anal. Calcd. for $C_{15}H_7N_5O_6$ (353): C, 51.00; H, 1.98; N, 19.83. Found: C, 50.96; H, 1.95; N, 19.80.

3-(2-Oxo-2*H*-benzo[*h*]chromen-3-yl)-6*H*,8*H*-pyridazine-5,7-dione (**3g**) (**entry 7**).

This compound has the following properties: m.p. 268-270 °C; IR (KBr, cm^{-1}): 1568 (C=C), 1683 (-CONH-), 1712 (lactone -C=O) and 3412 (-NH-). ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.95 (s, 1H, pyridazine), 7.1–8.1 (m, 5H, Ar-H), 8.4 (d, 1H, C_{10}, J = 8 Hz), 8.9 (s, 1H, C_4 of coumarin), 11.4 (s, 1H,-NHCONH-) and 12.8 (s, 1H, -NHCO-); Mass : m/z 358 (M^+).

Anal. Calcd. for $C_{19}H_{10}N_4O_4$: Found : C, 63.69; H, 2.81; N, 15.64%).

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