A facile one step synthesis of 3-(2-oxo-2*H*-chromen-3-yl)-indeno-[2,1-*c*]pyridazin-9-one

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3-Acetylcoumarins (**1**) on reaction with ninhydrin (**2**) in acetic acid followed by treatment of *in situ* formed 2-hydroxy-2-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl]indan-1,3-diones (**3**) with hydrazine hydrate resulted in the formation of corresponding 3-(2-oxo-2H-chromen-3-yl)-indeno[2,1-*c*]pyridazin-9-ones (**4**) in a single step with an excellent yields. The structures of newly synthesised compounds (**4**) were confirmed by unambiguous synthesis involving a two step process from 3-acetylcoumarins.

Keywords: 3-acetylcoumarins, ninhydrin, 3-(2-oxo-2H-chromen-3-yl)-indeno[2,1-*c*]pyridazin-9-one

Various reports established that the C-2 position of ninhydrin is more reactive to nitrogen, sulfur, oxygen and carbon-based nucleophiles.[1,2] Acid catalysed condensation of ninhydrin with various phenols and aromatic substrates (excluding ether) have been studied.[3-7] It was reported that amino C-alkyl, hydroxy- and alkoxy-phenols react with ninhydrin in refluxing acetic acid to produce monoarylated products and the mechanism of the reaction also has been postulated.[6]

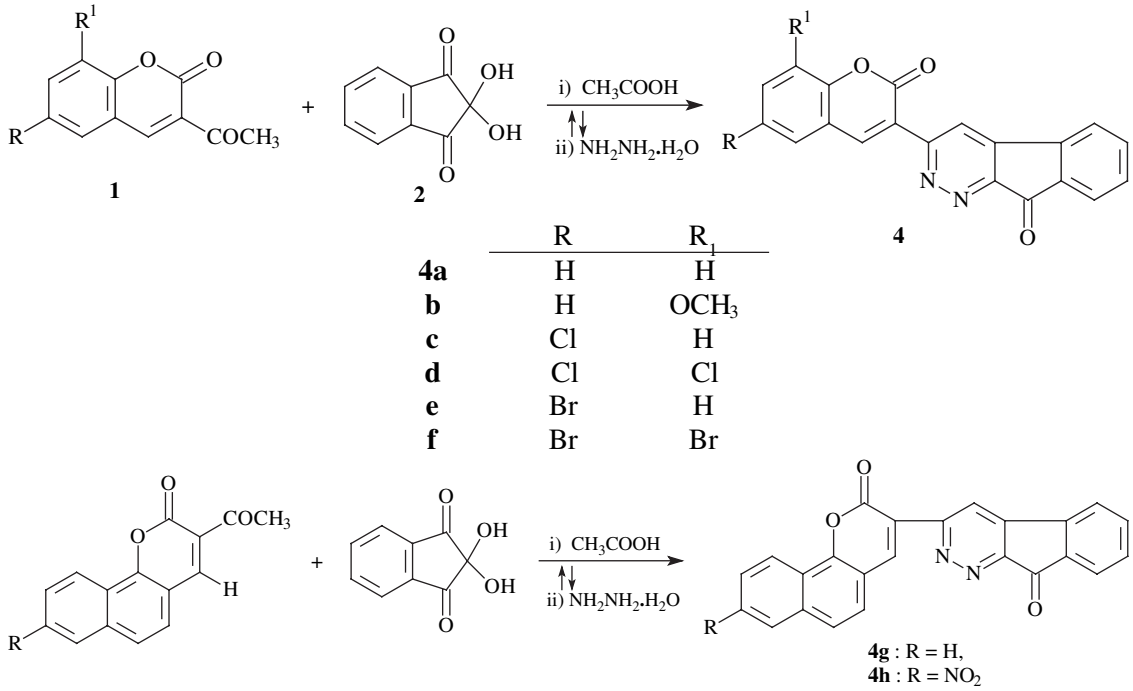
In continuation of our earlier work on the synthesis of heterocyclic systems derived from coumarin[7,8] we report here the facile one pot synthesis of 3-(2-oxo-2*H*-chromen-3-yl)indeno[2,1-*c*]pyridazin-9-one (**4**) in a single step from easily available starting materials like 3-acetylcoumarin, ninhydrin and hydrazine hydrate. We describe for the first time the easy and efficient one-pot preparation of indenopyridazinyl system at the 3rd position of coumarin. The procedure involves reaction of 3-acetylcoumarins with ninhydrin in glacial acetic acid followed by addition of hydrazine hydrate. The yields of the products (**4**) are better (84–90%).

In the one step synthesis, it is believed that 3-acetylcoumarins react with ninhydrin to yield corresponding intermediate aldol adducts 2-hydroxy-2-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)ethyl]indan-1,3-diones (**3**). These *in situ* formed intermediates subsequently reacts with hydrazine hydrate to give 3-(2-oxo-2*H*-chromen-3-yl)indeno[2,1-*c*]pyridazin-9-ones (**4**).

The first method is less time consuming involves a simple workup procedure and is of general applicability. The reaction is fairly general, easy and efficient and also devoid of any side products. The reaction takes place under mild conditions.

Method I

Compound **4** can also be synthesised by an alternative method involving condensation of 3-acetylcoumarin with ninhydrin in acetic acid to yield the corresponding 2-hydroxy-2-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl]indan-1,3-dione (**3**). These on reaction with hydrazine hydrate resulted in the formation of **4** via a 2 step process (method II) by cyclocondensation (yield 70–80%). The cyclocondensation proceeds in a chemoselective nucleophilic attack of NH_2NH_2 on >C=O groups of 1, 4-position rather than –C=O of ketone and carbonyl of ester of coumarin resulting in the formation of stable 6-membered heterocyclic pyridazinone derivatives. The products obtained by both the methods were found to be identical by their mixed m.p. measurements, Co-TLC and IR spectra.



Scheme 1

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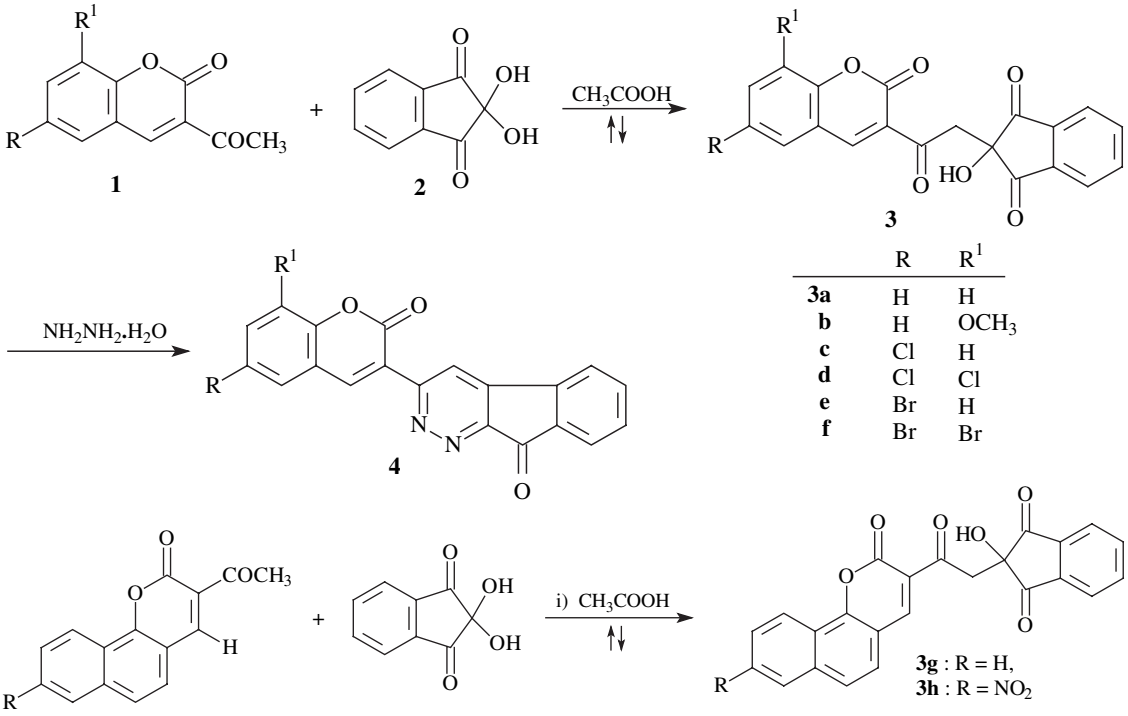

	R	R^1
3a	H	H
b	H	OCH_3
c	Cl	H
d	Cl	Cl
e	Br	H
f	Br	Br

Scheme 2

Method II

In the present investigation, method I was preferred over method II. This is due to the higher yields and shorter reaction time in method I. The structures **3** and **4** were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectra.

The reactions reported herein expand the scope of synthetic transformation and offer a new and convenient one step synthesis of 3-(2-oxo-2*H*-chromen-3-yl)indeno[2,1-*c*] pyridazin-9-ones. The characterisation data for some representative compounds (**3a–h** and **4a–h**) has been given. The IR spectra of compounds **4** showed prominent peaks 1562 (C=C), 1606 (–C=N–), 1690 (–C=O) and 1716 (lactone, –C=O), consistent with the assigned structures. The ^{1}H NMR ($CDCl_3$) spectrum of **4a** showed signals around δ 7.33–7.88 (m, 7H, aromatic), 8.25 (d, 1H, C_8–H, *J*=7.55 Hz), 8.66 (s, 1H, C_4 of coumarin) and 8.95 (s, 1H, pyridazine). In ^{13}C NMR ($CDCl_3$, δ ppm) spectrum of **4a** showed the signals at 189.73 (C of –C=O of pyridazinone) and 161.44 ('C' of lactone –C=O). The mass spectral analyses (70 eV) recorded the molecular ion peak at 326 (100%) for **4a**. The molecular ion under electron impact readily loses nitrogen and two molecules of carbonmonoxide to yield $(M-28)^+$ and (M-56) peaks, respectively.

The IR spectra of compounds **3** showed prominent peaks at 3377 cm^{-1} (OH), 1707 (lactone –C=O), 1678 (–C=O) and 1602 (–C=N–). The OH proton (D_2O exchangeable) appear around δ 8.59 in the NMR spectra. The methylene protons appear at δ 3.98 as a singlet. The mass spectrum of **3a** showed the molecular ion at *m/z* 348. In the mass spectra all the compounds gave molecular ion peaks. All the compounds were characterised on the basis of their spectra data and elemental analyses.

Experimental

Melting points were determined in open capillaries with a "Cintex" melting point apparatus, Mumbai, India and were uncorrected. The purity of the compounds was checked by TLC plates (E.Merck, Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-400 Spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-300 spectrometer (in δ ppm) using TMS as internal standard. Mass spectra (EI-MS) were determined on Jeol-D-300 spectrometer at 70 eV. Ninhydrin was procured from E.Merck, Mumbai, India. Acetic acid and hydrazinehydrate were procured from Loba chemicals, Mumbai, India. The 3-acetylcoumarins (**1**) were prepared by reported procedures.[9-10]

Synthesis of **4** *from 3-acetylcoumarin: typical procedure*

A mixture of 3-acetylcoumarin (0.940 g, 5 mmol) and ninhydrin (0.890 g, 5 mmol) was taken in 10 ml of glacial acetic acid was heated to reflux over a period of 3–4 hours. Upon cooling to room temperature and then hydrazin hydrate (98%), 0.34 ml(7.5 mmole) was added the reaction mixture was stirred for 4–5 h. The solid separated was filtered was dryness to give (**4a–h**), crystallised from methanol.

3-(2-Oxo-2H-chromen-3-yl)indeno[2,1-c]pyradazin-9-one (**4a**): Recrystallised from methanol, m.p. 295–297°C, yield 94%. IR (KBr, ν_{max} cm^{-1}): 1562 (–C=C), 1606 (C=N), 1690 (–C=O), 1716 (lactone (–C=O), ^{1}H NMR ($CDCl_3$, δ ppm): 7.33–7.88 (m, 7H, Ar–H), 8.25 (d, 1H, C_8–H, *J*=7.55 Hz), 8.66 (s, 1H, C_4 of coumarin) and 8.95 (s, 1H, pyridazine). EI-MS: 326 (M^+, 100%), 298 (20) and 270 (56).

3-(8-Methoxy-2-oxo-2H-chromen-3-yl)indeno[2,1-c]pyridazin-9-one (**4b**): Recrystallised from methanol, m.p. 235–237°C, yield 90%. IR (KBr): 1565 (C=C), 1599 (–C=N–), 1690 (–CO–, ketone), 1720 (lactone, –C=O), ^{1}H NMR ($CDCl_3$, δ ppm): 4.02 (s, 3H, $-OCH_3$), 7.17–7.31 (m,3H, Ar–H), 7.60–8.30 (m, 4H, Ar–H), 8.43 (s, 1H, C_4 of coumarin), 8.96 (s, 1H of pyridazine).

3-(6-Chloro-2-oxo-2H-chromen-3-yl)indeno[2,1-c]pyridazin-9-one (**4c**): Recrystallised from methanol, m.p. >300°C, yield 86%. IR (KBr): 1559 (C=C), 1607 (–C=N), 1679 (–CO–, ketone), 1726 (lactone, –C=O), ^{1}H NMR ($CDCl_3$, δ ppm); 7.26–8.36 (m, 7H, Ar–H), 8.66 (s, 1H, C_4 of coumarin), 8.91 (s, 1H of pyridazin).

3-(6-Bromo-2-oxo-2H-chromen-3-yl)indeno[2,1-c]pyridazin-9-one (**4e**): Recrystallised from methanol, m.p. >300°C, yield 92%. IR (KBr): 1560 (C=C), 1606 (–C=N), 1690 (–CO, ketone), 1725 (lactone, –C=O), ^{1}H NMR ($CDCl_3$, δ ppm): 7.26–7.35 (m, 3H, Ar–H), 7.71–7.84 (m, 4H, Ar–H), 8.66 (s, 1H, C_4 of coumarin), 8.89 (s, 1H of pyridazine).

3-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)indeno[2,1-c]pyridazin-9-one (**4f**): Recrystallised from methanol, m.p. >300°C, yield 84%. IR (KBr): 1559 (C=C), 1603 (–C=N), 1690 (–CO, ketone), 1727 (lactone, –C=O), ^{1}H NMR ($CDCl_3$, δ ppm): 7.60–7.91 (m, 5H, Ar–H), 8.22 (d, 1H, C_7 of coumarin, *J*=8 Hz), 8.2 (s, 1H, C_4 of coumarin), 8.89 (s, 1H of pyridazine).

3-(3-oxo-3H-benzo[f]chromen-2-yl)indeno[2,1-c]pyridazin-9-one (**4g**): Recrystallised from methanol, m.p. >300°C, yield 88%. IR (KBr): 1558 (C=C), 1619 (–C=N), 1690 (–CO, ketone), 1724 (lactone, –C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 7.53–8.00 (m, 7H, Ar–H),

Table 1 Physical and analytical data of 2-hydroxy-2-[2-oxo-2H-chromen-3-yl)-ethyl]-indan-1,3-dione (**3**) and 3-(2-oxo-2H-chromen-3-yl)-indeno[2,1-c]pyridazin-9-one (**4**)

Compd	R	Yield	M.p./°C	Microanalysis (Found)		
	R^1			C	H	N
3a	H	80	243–245	68.97	3.47	
	H			(68.95)	(3.46)	–
3b	H	78	235–237	66.67	3.73	
	OCH_3			(66.66)	(3.71)	–
3c	Cl	75	220–222	62.76	2.90	
	H			(62.73)	(2.87)	–
3d	Cl	70	215–217	57.58	2.42	
	Cl			(57.56)	(2.41)	–
3e	Br	72	217–219	56.23	2.60	
	H			(56.20)	(2.59)	–
3f	Br	74	210–212	47.46	1.99	
	Br			(47.45)	(1.98)	–
3g	–	75	233–235	72.36	3.54	
				(72.35)	(3.52)	–
3h	–	72	237–239	65.02	2.96	
				(65.00)	(2.95)	–
4a	H	94	295–297	73.62	3.09	8.58
	H			(73.61)	(3.00)	(8.55)
4b	H	90	235–237	70.78	3.39	7.86
	OCH_3			(70.76)	(3.38)	(7.85)
4c	Cl	86	>300	66.59	2.51	7.77
	H			(66.58)	(2.50)	(7.74)
4d	Cl	84	>300	60.78	2.04	7.09
	Cl			(60.76)	(2.00)	(7.00)
4e	Br	92	>300	59.28	2.24	6.91
	H			(59.25)	(2.22)	(6.90)
4f	Br	84	>310	49.62	1.67	5.79
	Br			(49.60)	(1.65)	(5.77)
4g	–	88	>300	76.59	3.21	7.44
				(76.58)	93.20)	(7.41)
4h	–	80	>300	68.41	2.63	9.97
				(68.40)	(2.61)	(9.96)

8.10 (d, 1H, C_8, *J*=8.6 Hz), 8.21 (d, 1H, C_{10}, *J*=7.23 Hz), 8.47 (d, 1H, C_5, *J*=8Hz), 8.81 (s, 1H, C_4 of coumarin), 9.85 (s, 1H, of pyridazine).

Typical procedure for the preparation of 2-hydroxy 2-[2-oxo-2 (2-oxo-2H-chromen-3-yl)-ethyl]-indan-1,3-dione (**3a–h**): A mixture of 3-acetylcoumarin (0.940 g, 5 mmol) and ninhydrin (0.890 g, 5 mmol) was taken in 10 ml of glacial acetic acid was heated to reflux over a period of 3–4 hours upon cooling to room temperature. The solid separated was filtered to give (**3a**) crystallised from methanol.

2-Hydroxy-2-[2-oxo-2-(2-oxo-2H-chromen-3yl)ethyl]indan-1, 3-dione (**3a**): Recrystallised from methanol, m.p. 243–245°C, yield 80%. IR (KBr): 1556 (C=C), 1602 (C=N–), 1678 (–C=O–, ketone), 1707 (lactone –C=O), ^{1}H NMR ($CDCl_3$, δ ppm), 3.98 (s, 2H, $–CH_2–$), 7.39–7.47 (m, 4H, Ar–H), 7.73–7.86 (m, 4H, Ar–H), 8.05 (s, 1H, C_4 of coumarin), 8.59 (s, 1H, –OH). EIMS: M^+ 348.

2-Hydroxy-2-[2-(8-methoxy-2-oxo-2H-chromen-3-yl)-2-oxoethyl] indan-1,3-dione (**3b**): Recrystallised from methanol, m.p. 235–237°C, yield 78%. IR (KBr): 1564 (C=C), 1602 (–C=N), 1676 (–CO–, ketone), 1703 (C=O), 1739 (lactone, –C=O), ^{1}H NMR ($CDCl_3$, δ ppm): 3.86 (s, 2H, $–CH_2–$), 4.0 (s, 3H, $–OCH_3$), 7.05–7.67 (m, 4H, Ar–H), 7.81–7.95 (m, 4H, 3Ar–H and OH, D_2O exchangeable) and 8.25 (s, 1H, C_4 of coumarin).

2-[2-(6,8-Dichloro-2-oxo-2H-chromen-3-yl)-2-oxoethyl]-2-hydroxy-indan-1,3-dione (**3d**): Recrystallised from methanol, m.p. 215–217°C, yield 70%. IR (KBr): 1556 (C=C), 1604 (C=N), 1680 (–C=O–, ketone), 1732 (lactone, –C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 3.99 (s, 2H, $–CH_2–$), 7.26–8.00 (m, 7H, Ar–H) and 8.36 (s, 1H, C_4 of coumarin).

2-[2-(6-Bromo-2-oxo-2H-chromen-3-yl)-2-oxoethyl]-2-hydroxy-indan-1,3-dione (**3e**): Recrystallised from methanol, m.p. 217–219°C, yield 72%. IR (KBr): 1554 (C=C), 1602 (–C=N–), 1678 (–C=O–, ketone), 1734 (lactone, –C=O), ^{1}H NMR ($CDCl_3$, δ ppm): 3.9 (s, 2H, $–CH_2–$), 7.26–7.30 (m, 2H, Ar–H), 7.72–8.08 (m, 6H, Ar–H), 8.35 (s, 1H, C_4 of coumarin).

2-Hydroxy-2-[2-oxo-2-(3-oxo-3H-benzo[f]chromen-2-yl)ethyl] indan-1,3-dione (**3g**): Recrystallised from methanol, m.p. 233–235°C, yield 75%. IR (KBr): 1554 (C=C), 1593 (–C=N–), 1670 (–C=O, ketone), 1712 (lactone, –C=O).

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).

Received 10 January 2005; accepted 25 February 2005
Paper 05/2998

References

1 S. Ruhemann, *Trans. Chem. Soc.,* 1910, **97**, 433.
2 (a) N. Peet, E.W. Huber and J.C. Huffman, *J. Heterocyl. Chem.,* 1995, **32**, 33; (b) D.St.C. Black, M.C. Bowyer, G.C. Condie, D.C. Craig and N. Kumar, *Tetrahedron,* 1994, **50**, 10983; (c) S.K. Kundu, A. Pramanik and A. Patra, *Synlett,* 2002, **5**, 823; (d) J.L. Bullington and J.H. Dodd, *J. Org. Chem.,* 1993, **58**, 4833; (e) J.N. Usmani and S.M. Ismail, *Pak. J. Sci. Ind. Res.,* 1987, **30**, 89.
3 J-P Poupelin, G. Saint-Ruf, J-C Perche, B. Laude, G. Narcisse, F. Bakri-Logesis and F. Hubert, *Eur. J. Med. Chem.,* 1980, **15**, 253; J-P Poupelin, G. Saint-Ruf, J-C Perche, R. Lacroix, G. Uchida-Ernouf, G. Narcisse and F. Hubert, *Eur. J. Med. Chem.,* 1979**, 14**, 171.
4 (a) G. Schmitt, N.An. Dinh, J-P Poupelin, J. Vebrel and B. Laude, *Synthesis,* 1984, 758; (b) T. Yamazaki and Takizawa, *Tetrahedron,* 1972, **28**, 4675.
5 H.N. Song, M.R. Seong, J.S. Son and J.N. Kim, *Synth. Commun.,* 1998, **28**, 1865.
6 D.A. Klumpp, S. Fredrick, S. Lau, K.K. Jin, R. Bau, G.K.S. Prakash and G.A. Olah, *J. Org. Chem.,* 1999, **64**, 5152.
7 G.A. Olah, *Friedel-Crafts and Related Reactions*, Wiley New York, 1964, Vol. 2, 597-640.
8 V.R. Rao, G.M. Rao, V.R. Kumar and V.A. Vardhan, *Phosphorus, Sulfur Silicon,* 1996, **47**, 113.
9 (a) R. Dahiya and H.K. Pujari, *Ind. J. Chem.,* 1986, **25B**, 966; (b) V.A. Vardhan and V.R. Rao, *Ind. J. Chem.,* 1997, **36B**, 1085.
10 (a) C.F. Koelsch, *J. Am. Chem. Soc.,* 1950, **72**, 2993; (b) V. R. Rao and T.V. P. Rao, *Ind. J. Chem.,* 1986, **25B,** 413.
11 C.V. Yelamaggad, U.S. Hiremath and B.V. Badami, *Ind. J. Chem.,* 1993, **32B**, 848.