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ORIGINAL PAPER

Synthesis, Characterization and Structural Conformation Studies of 2-Amino-3-ethoxycarbonyl-4-(4′-methoxy Phenyl)-4H-pyrano-[3,2-c]-chromene-6-methyl-5-one

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Abstract 2-amino-3-ethoxycarbonyl-4-(4′-methoxy Phenyl)-4H-pyrano-[3,2-c]-chromene-6-methyl-5-one was synthesized by the two-component reaction of 6-methyl-4-hydroxy coumarin with 4′-methoxy-2-cyano cinnamate, which was synthesized by Knoevenagel reaction with 88% yield. The compound obtained was characterized by spectroscopic techniques and confirmed by X-ray crystallographic studies. The crystallographic data analysis reveals that the title compound crystallizes in the triclinic space group $P\overline{1}$ with cell parameters $a = 7.7750(8)$ Å, $b = 9.0310(6)$ Å, $c = 15.6120(17)$ Å, $\alpha = 77.249(7)°$, $\beta = 115.860(3)°$, $\gamma = 70.139(7)°$, $V = 1{,}003.0(16)$ Å^3 for $Z = 4$. The structure has been solved by direct methods and refined to $R1 = 0.0552$ for 3,164 observed reflections with $I > 2\ \sigma(I)$. The pyran ring is in a flattened boat conformation. The carbonyl group is oriented in a *-synperiplanar(cis)* conformation.

Keywords Knoevenagel reaction · Crystal structure · Flattened boat · Hydrogen bonds

Introduction

4-Hydroxycoumarin comprises the structural nucleus of large number of important drug entities. 4-Hydroxycoumarins, a diverse class of natural products, possess a wide range of biological activities[1] including anti-coagulant,[2] fungicides,[3] anti-inflammatory,[4] anti-tumour agents[5] and HIV protease inhibition effects.[6] It forms the key intermediate for the extensive use as oral anti-coagulants[7] and rodenticides.[8] Chromene derivatives can be used as immuno modulators and for the prophylaxis and treatment of different diseases of connective tissues, diabetes, psoriasis, anti-viral, ulcerous colitis and chronic hepatitis. Several natural or synthetic coumarins with various hydroxyl and other substituents were found to inhibit lipid peroxidation and to scavenge hydroxyl radicals and superoxide anions.[9] 4H-Chromenes with amino and cyano groups are also the synthons of some special natural products.

In continuation of the search for such potent molecules and as a part of our ongoing research, we planned to synthesize the hybrid structure having the lipophilic functionality on the pyran ring. We selected 4-OCH_3 as an electron donating group. The current work highlights the synthesis as well as the crystallographic studies of the important coumarin scaffold. The title compound was synthesized by the reaction of 4-hydroxycoumarin and ethyl 4′-methoxy-2-cyanocinnamate in the presence of piperidine as a base catalyst. Ethyl-4′-methoxy-2-cyanocinnamate was prepared by performing Knoevenagel reaction of 4-methoxy benzaldehyde with ethylcyanoacetate in quantitative yield. The structure of the title compound was established on the basis of Fourier transform infrared (FTIR) absorption spectroscopy, NMR and elemental analysis and finally confirmed by X-ray crystallography.

Experimental

The melting point was determined in an open capillary melting point apparatus. The FTIR absorption spectrum

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was recorded on Shimadzu FTIR-8400 spectrometer (KBr Pellet sample technique, 400–4,000 cm^{-1} frequency range). ^1H NMR spectrum was recorded on a Bruker AC 300 MHz FT–NMR spectrometer where TMS was used as internal reference and $DMSOd_6$ as solvent (chemical shifts in δ values, J in Hz). Mass spectrum was obtained using a Jeol SX 102/DA-6000 spectrometer (for FAB). Elemental analysis was done on CHN EA 1108 Elemental Analyser. Analytical TLC was performed on 0.25 mm silica gel plates (Merck 60 F_{254}) by using solvent system ethylacetate:Hexane (4:6).

Preparation of Ethyl 2-cyano-3-(4-methoxy phenyl) acrylate:

In a clean dry beaker, 4-methoxy benzaldehyde (2.72 g, 0.01 mol) was taken and was cooled to 5° C. Ethyl cyano acetate (1.98 g, 0.02 mol) was added dropwise. Piperidine (0.3 ml) was added immediately as a base catalyst. After thorough mixing and keeping at room temperature, the reaction mass was poured in to ice cold water, filtered and washed with water, dried and recrystallized from methanol. Yield: 88%. (Scheme 1)

IR (KBr): CH str. (assym.) 2,925 cm^{-1}, C=N str. 1,737 cm^{-1}, Aromatic C=C str. 1,451 cm^{-1}; 1,528 cm^{-1}; substituted phenyl ring str. 742 and 769 cm^{-1}.

^1H NMR (300 MHz): δ 1.36(*t*, 3H, CH_3); δ 3.81 (*s*, 3H, CH_3); δ 4.19(*q*, 2H, CH_2); δ 6.71 (*d*, 2H, J = 9 Hz & 1.8 Hz, phenyl-H); δ 7.14 (*d*, 2H, J = 9 Hz & 1.8 Hz, Phenyl-H). FAB Ms m/z (%) = 232 [M^{+1}].

Anal. Calcd. for $C_{13}H_{13}NO_3$ (2312): C = 67.52%, H = 5.67%, N = 6.06%, O = 20.76%; Found: C = 67.6%, H = 5.68%, N = 6.01%, O = 20.03%.

Preparation of 2-amino-3-ethoxycarbonyl-4-(4-methoxy Phenyl)-4H-pyrano-[3,2-c]-chromene-6-methyl-5-one

A mixture of 4-hydroxy-6-methyl coumarin (1.76 g, 0.01 mol) and Ethyl 2-cyano-3-(4-methoxy phenyl) acrylate (2.17 g, 0.01 mol) in absolute ethanol (30 ml) and piperidine (0.5 ml) was added. The mixture was refluxed on a steam bath for 7 h. The solution was cooled at room temperature for overnight. The separated solid product was collected and washed with chilled methanol and filtered. The solid product was then crystallized from DMF. Yield 37%, m.p.200° C. (Scheme 2)

IR (KBr): Amine, > NH str 3,417 cm^{-1}; CH str (asym) 2,925 cm^{-1}, C=O str. 1,739 cm^{-1}, C=O str.(pyran ring) cm^{-1}; Aromatic C=C str. 1,452 cm^{-1}; C-N str. 1,523 cm^{-1}; substituted phenyl ring str. 750 & 763 cm^{-1}.

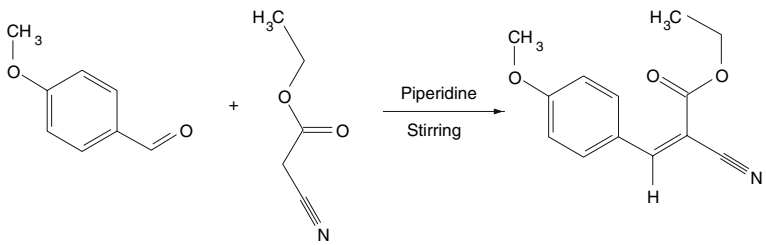
^1H NMR (300 MHz): δ1.31(*t*, 3H, CH_3); δ 2.356 (*s*, 3H, CH_3); δ 3.726 (*s*, 3H, CH_3); δ 4.17(*q*, 2H, CH_2); δ 5.17 (*s*, 1H); δ 6.52 (*s*, broad, 2H, NH_2); δ 7.23 (*m*, 4H, J = 9 Hz & 1.8 Hz, phenyl-H); δ 7.46 (*m*, 4H, Phenyl-H).

FAB Ms m/z (%) = 400[M^{+1}], 368(100%) (Base peak).

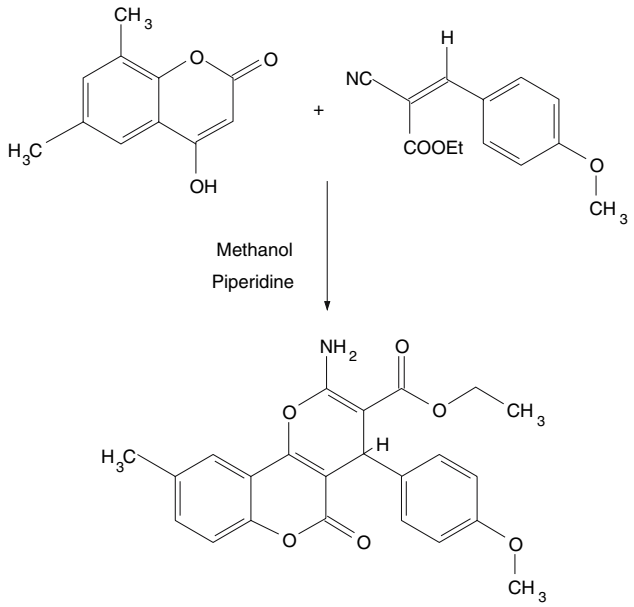
Anal. Calcd. for $C_{23}H_{21}NO_6$ (407.4): C = 67.80%; H = 5.20%; N = 3.44%; O = 16.50; Found: C = 67.89%; H = 6.28%. N = 3.39%; O = 16.50%.

Crystal Structure Determination and Refinements

A single crystal of the title compound with dimensions 0.25 × 0.25 × 0.2 mm was chosen for an X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with a normal focus, 3 kW sealed X-ray source [graphite monochromated MoK_α]. The crystal to detector distance is fixed at 120 mm with a detector area of 441 × 240 mm^2. A total of 36 frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 400 s. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5°. Image processing and data reduction were done using Denzo.[10] The reflections were merged with Scalepack. All of the frames could be indexed using a primitive triclinic lattice. The structure was solved by direct methods using SHELXS-97.[11] All the non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement using SHELXL-97 [11] with isotropic temperature factors for all the atoms converged the residuals to $R_1 = 0.1547$. Refinement of non-hydrogen atoms with anisotropic parameters was started at this stage. The hydrogen atoms were placed at chemically acceptable positions and were allowed to ride on the parent atoms. Refinement of 275 parameters with



Scheme 1 First reaction scheme



Scheme 2 Second reaction scheme

3,164 unique reflections converged the residuals to $R_1 = 0.0552$. The details of the crystal data and refinement are given in Table 1.[1]

Results and Discussion

Spectroscopic Analysis

The FTIR spectrum reveals the presence of all the functional groups present in the molecule. Here, the methylene group has asymmetric and symmetric C–H stretching vibration modes which occur near 2,926 cm^{-1} and 2,853 cm^{-1}. The bands due to the aromatic system occur near 1,600 cm^{-1}, 1,580 cm^{-1}, 1,530 cm^{-1} and 1,450 cm^{-1}. The out of plane wagging vibrations for the aromatic system are observed at 815 cm^{-1} and 756 cm^{-1}. The C=N stretching band is observed at 2,235 cm^{-1} in the intermediate product. In the final product, the peak at 2,235 cm^{-1} disappears and formation of new broad peak at 3,417 cm^{-1} indicates the presence of amino group. Carbonyl of ethyl ester and pyran ring appears at 1,739 cm^{-1} and 1,679 cm^{-1}.

In ^{1}H NMR, due to the presence of ethyl group triplet and quartets were observed. The methyl protons show signals at $\delta = 2.356$ ppm and OCH_3 shows singlet at 3.726 ppm. Stereogenic center shows a sharp singlet at $\delta = 5.17$ ppm. Aromatic protons appeared at $\delta = 7.23$ ppm and $\delta = 7.46$ ppm. The mass spectrum shows the M^+ peak at 408 m/e and the base peak at 368 m/e. The elemental analyses values are in good agreement with the theoretical values.

Table 1 Crystal data and Structure refinement table

CCDC Deposition Number	CCDC 615274
Empirical formula	$C_{23}H_{21}NO_6$
Formula weight	407.41
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Cell dimensions	$a = 7.7750(8)$Å
	$b = 9.0310(6)$ Å
	$c = 15.6120(17)$ Å
	$\alpha = 77.249(7)°$
	$\beta = 81.890(3)°$
	$\gamma = 70.139(7)°$
Volume	1003.0(16) Å^3
Z	2
Density(calculated)	1.349 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F_{000}	428
Crystal size	0.25 × 0.25 × 0.2mm
Theta range for data collection	2.44°–25.03°
Index ranges	$-9 \le h \le 9$
	$-9 \le k \le 10$
	$-17 \le l \le 18$
Reflections collected	4783
Independent reflections	3164 [R(int) = 0.0238]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3164 / 0 / 275
Goodness-of-fit on F^2	1.062
Final R indices [$I > 2\ \sigma(I)$]	$R1 = 0.0552$, $wR2 = 0.1639$
R indices (all data)	$R1 = 0.0657$, $wR2 = 0.1800$
Extinction coefficient	0.042(8)
Largest diff. peak and hole	0.296 and –0.203 e.Å^{-3}

Table 2 gives the list of bond distances and bond angles of non-hydrogen atoms respectively. The bond lengths and bond angles are in good agreement with the standard values. Fig. 1 represents the ORTEP [12] of the molecule with thermal ellipsoids drawn at 50% probability. Fig. 2 depicts the packing of the molecules when viewed down the b axis. The X-ray crystal structure determination shows that the interatomic distances 1.343(3) Å for C3–C8 and 1.356(3) Å for C5–C6 are near to that of a typical C–C double bond (1.34 Å). The bond angles for C3–C8–O7, C8–C3–C4, C4–C5–C6 and C5–C6–C7 are 122.67(17)°,

[1] "CCDC 615274 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033. email: deposit@ccdc.cam.ac.uk"

Table 2 Bond Lengths (Å) and Bond Angles (°)

Atoms	Length	Atoms	Length
O1–C14	1.374(2)	C11–C12	1.397(3)
O1–C2	1.377(2)	C11–C15	1.502(3)
C2–O16	1.208(2)	C12–C13	1.374(3)
C2–C3	1.445(3)	C13–C14	1.387(3)
C3–C8	1.343(3)	C18–O19	1.224(3)
C3–C4	1.508(3)	C18–O20	1.342(2)
C4–C5	1.517(3)	O20–C21	1.447(3)
C4–C23	1.535(3)	C21–C22	1.488(4)
C5–C6	1.356(3)	C23–C24	1.378(3)
C5–C18	1.444(3)	C23–C28	1.382(3)
C6–N17	1.334(3)	C24–C25	1.383(3)
C6–O7	1.382(2)	C25–C26	1.381(3)
O7–C8	1.365(2)	C26–O29	1.376(3)
C8–C9	1.440(3)	C26–C27	1.377(3)
C9–C14	1.389(3)	C27–C28	1.388(3)
C9–C10	1.396(3)	O29–C30	1.426(3)
C10–C11	1.383(3)		

Atoms	Angle	Atoms	Angle
C14–O1–C2	121.67(15)	C10–C11–C12	118.30(19)
O16–C2–O1	116.61(17)	C10–C11–C15	120.9(2)
O16–C2–C3	125.16(18)	C12–C11–C15	120.8(2)
O1–C2–C3	118.23(17)	C13–C12–C11	121.84(19)
C8–C3–C2	118.85(17)	C12–C13–C14	119.09(19)
C8–C3–C4	122.00(17)	O1–C14–C13	117.50(18)
C2–C3–C4	119.14(16)	O1–C14–C9	121.90(17)
C3–C4–C5	108.87(15)	C13–C14–C9	120.59(19)
C3–C4–C23	111.83(15)	O19–C18–O20	122.41(18)
C5–C4–C23	110.53(15)	O19–C18–C5	126.1(2)
C6–C5–C18	119.06(18)	O20–C18–C5	111.46(17)
C6–C5–C4	121.07(17)	C18–O20–C21	117.01(18)
C18–C5–C4	119.41(17)	O20–C21–C22	107.2(2)
N17–C6–C5	128.35(19)	C24–C23–C28	117.37(19)
N17–C6–O7	109.36(17)	C24–C23–C4	122.18(17)
C5–C6–O7	122.29(18)	C28–C23–C4	120.34(17)
C8–O7–C6	118.46(15)	C23–C24–C25	121.8(2)
C3–C8–O7	122.67(17)	C26–C25–C24	119.8(2)
C3–C8–C9	123.17(18)	O29–C26–C27	124.8(2)
O7–C8–C9	114.14(17)	O29–C26–C25	115.72(19)
C14–C9–C10	119.33(18)	C27–C26–C25	119.5(2)
C14–C9–C8	115.86(18)	C26–C27–C28	119.6(2)
C10–C9–C8	124.76(18)	C23–C28–C27	121.81(19)
C11–C10–C9	120.85(19)	C26–O29–C30	117.80(19)

122.00(17)°, 121.07(17)° and 122.29(18)° respectively, which illustrate that C3, C5, C6 and C8 all adopt sp^2 hybrid orbit to form C=C double bonds. The bond angle C6–O7–C8 = 118.46(15)° is nearer to 120°, which indicates that the O7 atom adopts sp^2 hybrid orbit to conjugate the intercyclic C=C bonds C5–C8 and C8–C3. The bond length

Table 3 Hydrogen-bonding geometry (Å.°)

D–H…*A*	*D*–H	H–*A*	*D*–*A*	*D*–H…*A*	Symmetry Codes
N17–H17B…O16	0.8600	2.1400	2.969(4)	161.00	1 + *x*, *y*, *z*
C25–H25…O29	0.9300	2.5900	3.518(5)	177.00	1 – *x*, –*y*, 2 – *z*

* The D–H and H–A distances are essentially standard values and are not derived from the experiment.

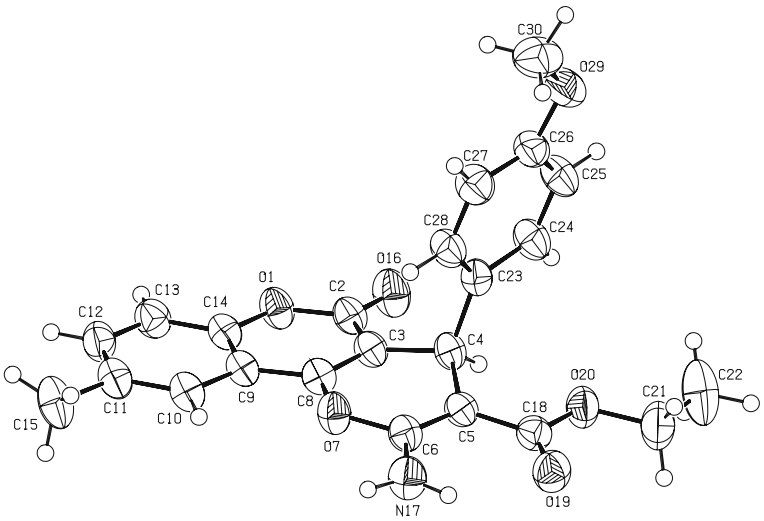


Fig. 1 ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability

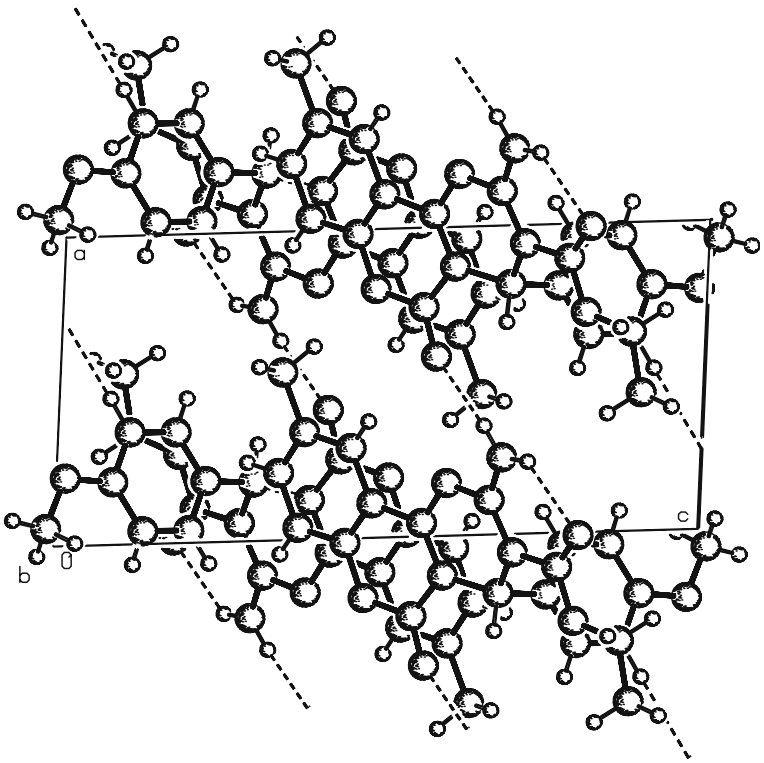


Fig. 2 Packing diagram of the molecules when viewed down the *b* axis. The dashed lines represent the hydrogen bonds

of C8–O7 (1.365(2) Å) is a little bit shorter than that of C6–O7 (1.382(2) Å) becuase of the conjugate effect. Due to the existence of a conjugated system, the C6–N17 bond length of 1.334(3) Å is shorter than the typical Csp^2–N bond distance [13]. The pyran ring [O1/C2/C3/C8/C9/C14] of the coumarin core is planar. A study of the torsion

angles, asymmetric parameters and least-squares plane calculations reveals that the pyran ring [C3/C4/C5/C6/O7/C8] in the structure adopts a flattened boat conformation with the atoms C4 and O7 deviating by –0.150(2) Å and –0.098(17) Å from the Cremer and Pople plane [14] defined by the atoms C3/C5/C6/C8. This is also confirmed by the puckering parameters Q = 0.2240(21) Å, θ = 73.60(54)° and ϕ = 176.7(6)°. Similar conformations were observed in Ethyl 2-amino-3-ethoxycarbonyl-7,8-dimethyl-4-[4-(methylsulfanyl)phenyl]-5-oxo-4H-pyrano[3,2-c]chromene-3-carboxylate [15] and Ethyl 9-amino-7-(4-methoxyphenyl)-7H-pyr-ano[3,2-c]coumarin-8-carboxylate [16]. The methoxyphenyl ring occupies a pseudo-axial position with respect to the pyran moiety with the dihedral angle being 84.26(1)°. This value is low when compared to the corresponding value of 89.85(9)° reported earlier [17]. The methoxy group lies in the plane of the parent phenyl ring as indicated by the torsion angle value of –0.4(3)° for C30–O29–C26–C27. The torsion angles C5–C4–C23–C24 = 118.7(2)° and C28–C23–C4–C3 = 64.0(3)° determine the conformation of the junction of the methoxyphenyl and the fused benzopyran moiety. The spatial arrangement of the carbonyl group with respect to the C6 = C5 bond adopts a *cis* conformation as indicated by the torsion angle value of –3.41(3)° for C6–C5–C18–O19. This orientation can probably be attributed to the intramolecular N–H…O hydrogen bonding involving the carbonyl atom O19. It is evident from the literature that in the ester substituted analogs the carbonyl oxygens generally adopt *sp/ap* conformations, while the carbamoyl oxygens adopt *anticlinal* conformation [18]. The structure exhibits both inter and intramolecular hydrogen bonds of the type C–H…O and N–H…O. These hydrogen bonds link the molecules into chains and help in stabilizing the crystal structure. The observed hydrogen bonds are listed in Table 3.

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