SYNTHESIS AND CRYSTAL STRUCTURE ANALYSIS OF 3 - (4 - METHOXYBENZYL) - 2, 3 – DIHYDRO - 4H – CHROMAN – 4 - ONE

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Abstract

3-(4-methoxybenzyl)-2,3-dihydro-4H-chroman-4-one($C_{17}H_{16}O_3$) was synthesized by refluxing 2'-Hydroxydihydrochalcone dissolved in ethanol with paraformaldehyde and 50% aqueous diethylamine. The compound is characterized by IR,^{1}HNMR, MS and X-ray diffraction studies. The X-ray structure analysis indicates that the crystal suffers from the positional disorder over two positions, atomC1 and C9 with required site occupancies of 0.590 and 0.410 leading to a conformational difference between the major and minor components. After applying similarity restraints, the final reliability index is 0.0275 for 2209 unique reflections .The crystal packing is stabilized by inter molecular C-H…O, C-H…π and π …π interactions.

Keywords: 3-Benzyl-4H-Chroman-4-one, Synthesis, Single Crystal XRD

Intermolecular interactions

Introduction

Homoisoflavanones belong to a small homogeneous group of naturally occurring oxygen heterocycles. The first homoisoflavanones to be isolated were eucomin and eucomol. Since then a large number of these compounds have been isolated from several genera within the Hyacinthaceae

family including *Eucomis, Merwilla, Ledebouria, Veltheimia* and *Drimiopsis*. The homoisoflavanones consist of a sixteen carbon skeleton which includes a chromanone, chromone or chromane ring system with a benzyl or benzylidene group at position C3 Naturally occurring homoisoflavanones that posses a 3-benzyl substituted chroman ring system as a common framework have been isolated from a wide range of natural sources and exhibit a variety of biological activities. Homoisoflavanones are also widely used as antioxidant, antiviral, antimutagenic, antiproliferative and antifungal agents. A variety of compounds having a benzopyran ring such as levcromakalim generally exhibit potent antihypertensive activity.

As a continuation of our efforts towards synthesizing and reporting the crystal structure of biologically active heterocyclic compounds, the title compound was prepared and its crystal structure is now reported. The synthesis of the compound was followed by subsequent spectroscopic analyses using IR, Mass and ^{1}H NMR techniques to confirm the presence of the supposed ring systems. The structure of the derivative 3-(4-methoxybenzyl)-2,3-dihydro-4H-chroman-4-one was verified by single crystal X-ray diffraction so that its supramolecular structure could be investigated in terms of possible intermolecular interactions.

Experimental

Synthesis

Experimental Procedure for the Preparation of 3-(4-methoxybenzyl)-2,3-dihydro-4H-chroman-4-one

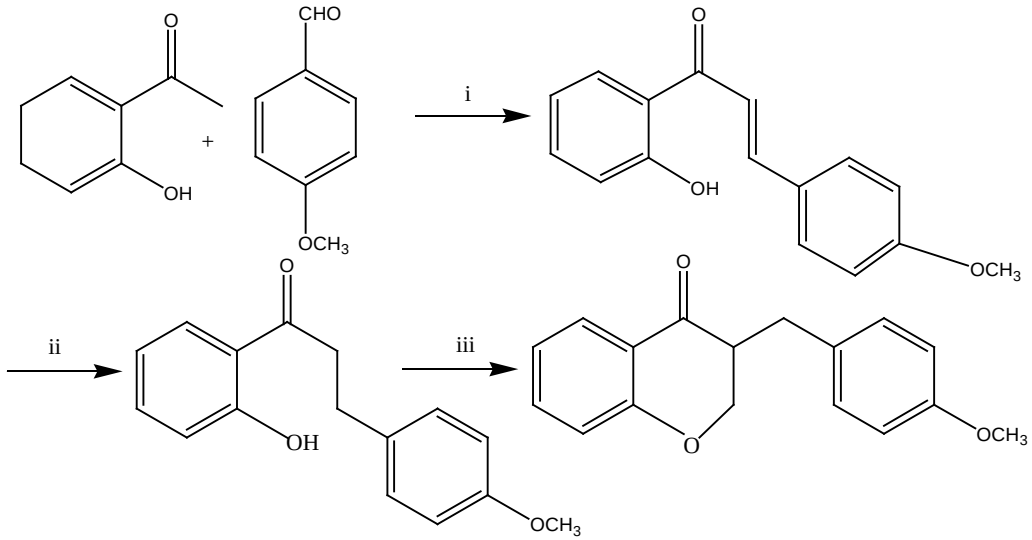
The strategy for the synthesis of 3-(4-methoxybenzyl)-2,3-dihydro-4H-chroman-4-one involved the preparation of 2'-hydroxychalcone intermediate by Claisen-Schmidt condensation. 4-methoxybenzaldehyde (leq) was reacted with 2'-hydroxyacetophenone (leq) in 40-50% of MeOH/KOH. The mixture was poured into crushed ice acidified with dilute hydrochloric acid and stirred well. The reaction mixture was kept in the refrigerator for overnight to precipitate 2'-Hydroxychalcone.

2'-hydroxychalcones, saturated ammonium formate solution [methanol:THF(1:1] and 10% Pd/C were refluxed for 90 minutes. The reaction mixture was filtered. The product which remained in the filtrate was isolated in good yield by dispersing the residue in water, extracting it with ethyl acetate, and drying over anhydrous Na_2SO_4 to obtain 2'-Hydroxydihydrochalcone.

2'-Hydroxydihydrochalcone was dissolved in ethanol and refluxed with paraformaldehyde and 50% aqueous diethylamine for 9 hrs. Ethanol was distilled off and the residue was taken up in ethyl acetate.Ethyl acetate was distilled off and the oily residue was column chromatographed over silica using pet ether: ethyl acetate(7:3) as eluent to get the 3-(4-methoxybenzyl)-2,3-dihydro-4H-chroman-4-one in 60-70% yield. The title

compound is characterized by spectroscopic and X-ray diffraction studies. The scheme for the synthesis is given below

Scheme



i) 40% w/v alcoholic KOH, rt, 12-36 h; ii) 10% Pd-C, $HCOONH_4$, MeOH-THF (1:1), reflux, 90 min iii) 50% v/v aq. diethylamine, $(HCHO)_n$, EtOH, reflux, 9 h.

Spectroscopic details

IR(c m-1)	MASS(m/z)	1H-NMR,400 MHz, solvent DMSO
1687 (C=O str) 1602 (C=C str) 2926 (C-H str)	M+268(20%),237,147, 121 (100%)	δ 4.3(dd,J=15.2, 4.4Hz,1H,2-H), δ 4.2(dd,J=9.2, 3.2Hz,1H,2-H), δ 2.6(m,2-H, 9'-H),δ 3.5(S,3H,4'-OCH3), δ 7.7(dd,J=7.6, 1.6Hz,1H)

Single crystal X-ray Crystallography

Single crystals of the title compound were grown using methanol as solvent by slow evaporation technique under ambient temperature. The crystal structure analysis has been determined by the X-ray diffraction method. The compound is known to crystallize in the monoclinic space group $P2_1/n$ and the unit cell parameters are, a = 8.449(5)Å, b = 6.575(5) Å, c = 24.699(5) Å, β= 97.265(5)° , V = 1361.1(13) $Å^3$, Z=4, Dx= 1.309 Mg/m^3. The X-ray diffraction data for the title compound was collected on a Bruker Smart CCD Area Detector, using MoKα(λ = 0.71073Å) radiation. Intensity data were collected up to a maximum of 24° in the ω–φ scan mode. The data were reduced using SAINT . The structure was solved by direct methods using SIR92 and refined by difference Fourier synthesis using

SHELXL97. The positional and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement. A total of 11770 reflections were collected, resulting in 2209 [R(int) = 0.0275] independent reflections of which the number of reflections satisfying $I>2\sigma(I)$ criteria was 1676. The crystal suffers from the positional disorder over two positions, atomC1 and C9 with required site occupancies of 0.590 and 0.410 leading to a conformational difference between the major and minor components. After applying similarity restraints, the final reliability index is 0.0275 for 2209 unique reflections.The R factor for observed data finally converged to R1 = 0.0382, wR2 = 0.0914. Molecular diagrams were generated using ORTEP-3. The mean plane calculation was done using the program PARST.

Table.1 Crystal data and structure refinement for the title compound

Empirical formula	$C_{17}\ H_{16}\ O_3$
Formula weight	268.30
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 8.449(5) Å, b = 6.575(5) Å , c = 24.699(5)Å α = 90.000(5)° , β= 97.265(5)° , γ= 90.000(5)°
Volume	1361.1(13) $Å^3$
Z, Calculated density	4, 1.309 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	568
Crystal size	0.30 x 0.25 x 0.20 mm
Theta range for data collection	2.47 to 24.33°
Limiting indices	-9<=h<=9, -7<=k<=7, -26<=l<=28
Reflections collected / unique	11770 / 2209 [R(int) = 0.0275]
Completeness to theta = 24.33	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9824 and 0.9038
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2209 / 18 / 202
Goodness-of-fit on F^2	1.038
Final R indices [I>2σ (I)]	R1 = 0.0382, wR2 = 0.0914
R indices (all data)	R1 = 0.0543, wR2 = 0.1007
Extinction coefficient	0.0030(10)
Largest diff. peak and hole	0.184 and -0.157 $e.A^{-3}$

Table2. Non-bonded interactions and possible hydrogen bonds (Å, ◦).
(D-donor; A-acceptor; H-hydrogen)

D—H· · ·A	D—H	H· · ·A	D· · ·A	D—H· · ·A
C9-H9A…O2(i)	0.98	2.56	3.2841	131
C15-H15...Cg(ii)	0.93	2.94	3.8095	153
Cg…Cg (iii)			3.588	

Symmetry code: (i) 1-x,1-y,-z (ii) 1-X,-Y,-Z (iii) -X,1-Y,-Z

Results and Discussion

Crystal structure analysis

Summary of the crystallographic data and other structure refinement parameters of the compound are shown in Table.1. Table.2 shows the respective hydrogen bond interactions of the compound. The ORTEP view of the molecule with atomic labeling (thermal ellipsoids drawn at 50% probability) is shown in Figure 1. Figure.2 and Figure 3 shows the packing of molecules in the crystal structure.

Conformational Features

In the compound, the fused pyranone ring is substituted with the benzyl ring at C9 chiral carbon atom and is positioned equatorially to the chromanone ring. The dihedral angle between the planes of the benzyl and chromanone rings is 83.92°.The 4-aryl substituent (methoxy group) adopts a anti periplanar configuration with respect to C14–O3 bond(Torsion angle C(13)- C(14)- O(3) - C(17) = -172.08°). The fused pyranone ring with a chiral C9 atom at the point of substitution of a benzyl ring (C10-C16) is significantly puckered and adopts a conformation which is best described as half-chair form. The ring puckering parameters for the pyranone ring are Q(2) = 0.3789 Å., Q(3) = 0.3160 Å, φ= 81.0833° , θ = 50.17 ° and puckering amplitude Q_T= 0.4934 Å respectively. All other bond lengths and bond angles are in the normal range.

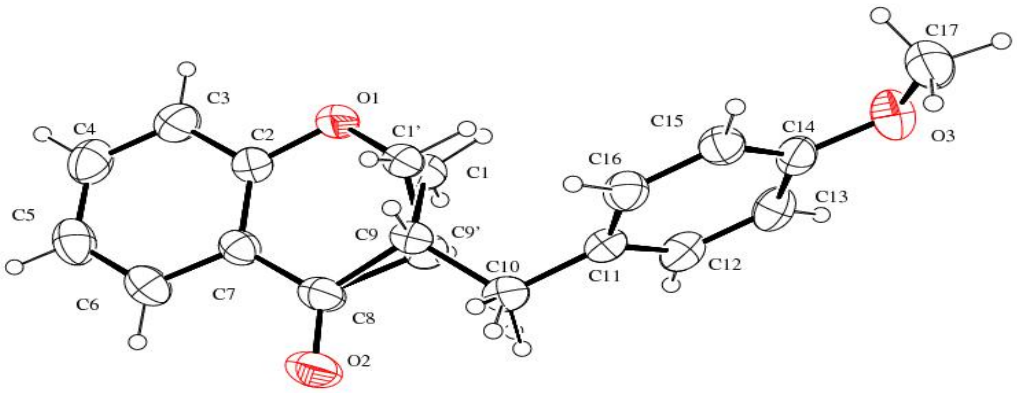


Figure 1. Ortep view of the title compound, showing 50% probability ellipsoids and the atom numbering scheme

Packing Features

The crystal structure is primarily stabilized by some interesting features that comprise intermolecular C–H. . . O interactions. An intermolecular C–H. . . O interaction results in the formation of an inversion dimer motif of graph set $R^2_2(8)$ as shown in figure.2.

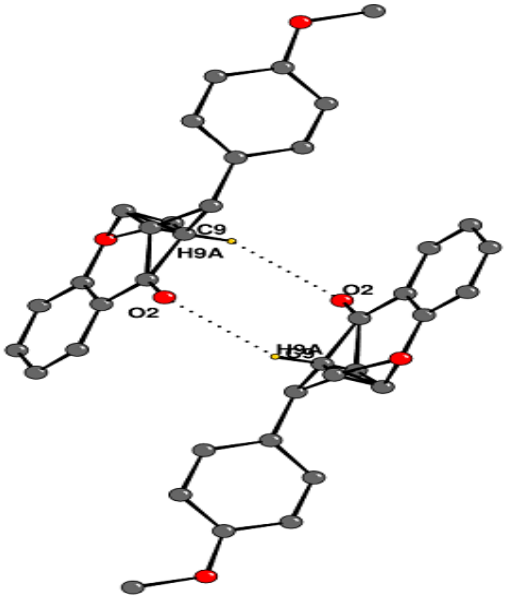


Figure.2 An intermolecular C–H. . . O interaction forming an inversion dimer motif of graph set $R_2^2(8)$

The molecular packing is further stabilized by π- π stacking interactions between the benzyl rings as the C11-C16 (-X,1-Y,-Z) is disposed at a distance of 3.588(3) Å. In addition, π - ring interactions of the type C–H. . . Cg (Cg being the centroid of the rings) are also observed in the crystal structure.

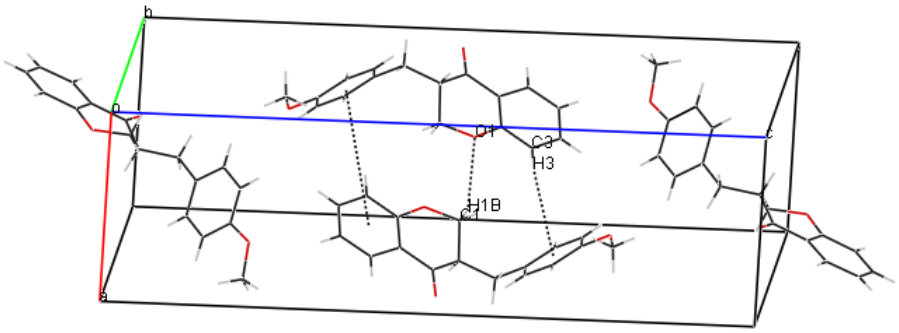


Figure 3. A unit cell packing of the title compound showing C-H…O, *Cg…Cg* and C-H… *Cg* interactions with dotted lines.

Conclusion

The present work reports the synthesis and X-ray structure analysis of homoisoflavanone derivative. The formation of the chroman-4-one moiety was confirmed by analytical data. The X-ray structure analysis indicates that the crystal suffers from the positional disorder over two positions, atomC1 and C9 with required site occupancies of 0.590 and 0.410 leading to a conformational difference between the major and minor components. The fused pyranone ring with a chiral C9 atom at the point of substitution of a benzyl ring (C10-C16) is significantly puckered and adopts a half-chair form conformation. The crystal structure is primarily stabilized by intermolecular C–H. . . O interactions. An intermolecular C–H. . . O interaction results in the formation of an inversion dimer motif of graph set $R_2^2(8)$. The molecular packing is further stabilized by π- π stacking interactions between the benzyl rings. In addition, π - ring interactions of the type C–H. . . Cg are also observed in the crystal structure.

Supplementary Material

The CIF file was deposited at the Cambridge Crystallographic Data Centre, The deposition number is CCDC-**873083.** These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif , by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK

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