#### **ORIGINAL PAPER**



# (Z)-3-(4-(Dimethylamino)benzylidene)thiochroman-4-one: Synthesis, Crystal Structure and Molecular Modelling Using Density Functional Theory

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#### Abstract

The title compound  $C_{18}H_{17}NOS$  was synthesized by condensation of thiochroman-4-one with 4-dimethylaminobenzaldehyde. The possible existence of the 3-(4-(Dimethylamino)benzylidene)thiochroman-4-one (*E*)- and (*Z*)-geometrical isomers was investigated using B3LYP/6-31G\*\*. Crystallographic and vibrational data are compared with the results of Density Functional Theory (DFT) B3LYP/6-31G\*\* level. Bond orders were estimated using the NBO calculation method correlating with changes in the bond length. To explain deviation of an ideal molecular geometry, the concept of non-equivalent hybrid orbitals was invoked. The studies of X-ray diffraction revealed strong intermolecular interactions between dimers of the compound connected to each other through dipole–dipole interactions S–C, N–C y O–C in the absence of hydrogen bonding.

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#### **Graphical Abstract**

In this report, a study of the structural characterization of (Z)-3-(4-(dimethylamino)benzyliden)thiochroman-4-one is carried out by spectroscopic methods, single-crystal X-ray diffraction and functional density calculations.



Keywords (Z)-3-(4-(Dimethylamino)benzylidene)thiochroman-4-one · Crystal structure · DFT calculations

#### Introduction

The 3-benzylidenethiochroman-4-ones are compounds structurally analogous to the homoisoflavonoids with a sulfur atom in the pyran-4-one ring. There are examples in the literature of some homoisoflavonoids with several biological properties of interest such as: anti-inflammatory [1], antifungal [2], antioxidant [3] and anticancer [4]. Compounds such as isothiochroman-4-ones analogous to compound (I) (Scheme 1), have been employed as intermediates in the synthesis of isoxazolines [5].

Some 3-benzylidenechroman-4-ones have been synthesized through a condensation reaction from a chroman-4-one substituted with an aromatic aldehyde in presence of an acid [6]. Others have been obtained using bases such as NaOH, KOH and piperidine [7–9]. Some papers have



Scheme 1 Synthesis of (*Z*)-3-(4-(Dimethylamino)benzylidene)thiochroman-4-one (I)

reported several isomerizations of 3-benzylidenechroman-4-onas and 3-benzylidenethiochroman-4-ones, succeeding in differentiating by NMR <sup>1</sup>H the isomers *E* and *Z*, locating the signal of the vinyl proton in the spectrum with the value of it respective coupling constant [10, 11]. The effect of the substituent attached to the phenyl of the benzylidene moiety play an important role in the crystalline packing of these aromatic compounds. Depending on the electronic nature of the substituents, face-to-face  $\pi$ - $\pi$  interactions, face-to-face  $\pi$ -stacking and *syn*-HH (*syn*-head-to-head) products have been found in [2+2] photocycloaddition of (*E*)-3-benzylidenechroman-4-ones in crystalline state [12]. In this work, we report the synthesis, crystal structure and density functional calculations of (I).

# **Experimental**

## Synthesis of (I)

The title compound (I) was synthesized by a Claisen-Schmidt condensation from commercially available thiochroman-4-one (332 mg, 2 mmol) (Sigma-Aldrich) and 4-dimethylaminobenzaldehyde (355 mg, 2.4 mmol) (Riedel-de Haën) were dissolved in abs. ethanol (6 mL), and 40% aqueous KOH solution (4 mL) was slowly added at 0 °C [13]. The reaction mixture was stirred overnight; the course of the reaction was followed by TLC. After reaction completion, the mixture was poured into iced water and the orange precipitate formed, was filtered and dried (yield, 70%). Crystals of (I) suitable for X-ray diffraction analysis were grown by slow evaporation of a saturated chloroform solution of (Z)-3-(4-(Dimethylamino)benzylidene)thiochroman-4-one at room temperature (mp: 431–432 K). <sup>1</sup>H NMR  $(\delta \text{ ppm}, \text{CDCl}_3, 400 \text{ MHz})$ : 8.16 (d, 1H, Ar, J = 8.1 Hz),7.76 (s,1H, H–C=), 7.37 (d, 2H, Ar, J = 8.8 Hz), 7.21–7.30 (m, 3H, Ar), 6.73 (d, 2H, Ar, J=7.3 Hz), 4.22 (s, 2H, CH<sub>2</sub>),3.08 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (δ ppm, CDCl<sub>3</sub>, 125 MHz): 185.79 (C8), 151 (C14), 140.63 (C2), 138.81 (C10), 132.88 (C4), 132.51 (C7), 131.8 (C9), 130.25 (C12 and C16), 128.38 (C6), 127.73 (C3), 125.64 (C5 and C11), 112.01 (C13 and C15), 40.29 (C17 and C18), 29.59 (C1). GC-MS [EI 70 eV, m/z (abundance %)]: 295 (100), 278 (15), 158 (62), 147 (25), 134 (79), 115 (15).

### **Physical Measurements**

Melting point was determined using a Fisher-Johns Mel-Temp melting point apparatus. Proton and carbon nuclear magnetic resonance spectra (<sup>1</sup>H NMR and <sup>13</sup>C NMR) were obtained in a JEOL Eclipse Plus 400 spectrometer (400 MHz), using tetramethylsilane as the reference and deuterated chloroform as the solvent for <sup>13</sup>C NMR and <sup>1</sup>H NMR. The F-IR analysis was carried out in a Bruker Optik GmbH Model No-Tensor 27. Electron ionization (EI) mass spectra were recorded using a Hewlett-Packard 5917 A mass spectrometer (electron impact ionization 70 eV) linked to a Hewlett-Packard Series II 5890 gas chromatograph.

## X-Ray Crystallography

The X-ray crystallographic data were recorded on a Rigaku AFC-7S Mercury diffractometer with graphite monochromated Mo-K $\alpha$  radiation. SHELXTL was the program used to solve and refine the structure [14]. DIAMOND was the program used to graphics molecular [15]. A summary of the crystal data and other details concerning data collection and structure refinement are given in Table 1.

## **Computational Calculation**

The DFT based method was most suitable for the calculations for molecules of our interest in gas phase. All the calculations were performed using B3LYP Density Functional Theory method, a hybrid version of DFT and Hartree–Fock (HF) methods, in which the exchange energy from Becke's exchange functional is combined with the exact energy from Hartree–Fock theory. Along with the component exchange and correlation functional, Becke's three parameters define the hybrid functional, specifying the extent of the exact exchange mixed in. The geometry of the compounds were optimized at the semi-empirical method AM1, HF and B3LYP/6-31G\*\* level of theory. All the calculations were carried out using Gaussian 09 suits of program with its graphical interface Gaussview 5.0.8 [16].

## **Results and Discussion**

### **Molecular Structure and DFT Calculations**

Valkonen et al. synthesized and characterized by X-ray diffraction a series of 3-benzylidenechroman-4-ones and 3-benzylidenethiochroman-4-ones [17]. These studies revealed strong intermolecular interactions in the absence of hydrogen bonding. Several weak interactions of the types C–H···O, C–H··· $\pi$ , and  $\pi$ ··· $\pi$  determine the crystal packing and define the spatial orientation of the benzylidene group in (I), with torsion angles of 46–55° conformed by the planes formed by C2–C7 and C11–C16 atoms of phenyl rings, as shown in Fig. 1.

In Table 2 are summarized some representative bond lengths and angles calculated with B3LYP/6-31G\*\* and the corresponding experimental values, observing agreement between both sets of data. Differences did not exceed 0.030 Å for bond lengths (e.g., S1–C1) and 2° for the bond angles (C8–C9–C10). The six-membered thiopyran-4-one ring, conformed by S1/C1/C9//C8/C7/C2 atoms is not planar due to the flexibility of the C1 atom and the intermolecular forces, where the torsion angle Table 1Crystal data andstructure refinement forcompound (I)

Molecular formula	C <sub>18</sub> H <sub>17</sub> NOS
Molecular weight	295.380
Temperature (K)	293(2)
Wavelength (Å)	0.7107
Crystal system	Triclinic
Space group	$P\overline{1}$
Unit cell dimensions	
a (Å)	8.019(3)
b (Å)	9.701(4)
c (Å)	9.802(5)
α (°)	85.400(4)
β (°)	86.710(3)
γ (°)	77.420(3)
Volume (Å <sup>3</sup> )	741.190(545)
Ζ	2
Density (Mg/m <sup>3</sup> )	1.324
Absorption coefficient (mm <sup>-1</sup> )	0.216
<i>F</i> (000)	312
Crystal size (mm <sup>3</sup> )	$0.150 \times 0.275 \times 0.350$
Theta range for data collection (°)	2.09–27.71
Index ranges	$-9\!\le\!h\!\le\!9,-12\!\le\!k\!\le\!12,-12\!\le\!l\!\le\!12$
Reflections collected	8661
Independent reflections	2736 $[R_{\text{int}} = 0.0340]$
Completeness to theta $= 25.25^{\circ}$	94.5%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	
Refinement method	Full-matrix least-squares on $F^2$
Data/restraints/parameters	2.736/0/259
Goodness-of-fit on $F^2$	1.092
Final <i>R</i> indices $[I > 2\sigma(I)]$	$R_1 = 0.0523, wR_2 = 0.1289$
R indices (all data)	$R_1 = 0.0682, wR_2 = 0.1387$
Largest diff. peak and hole (e $Å^{-3}$ )	0.172 and -0.258



Fig. 1 Molecular structure of compound (I). Ellipsoids have been draw at 50% probability; hydrogen atoms shown as small spheres with arbitrary radii

C2–S1–C1–C9 is  $54^{\circ}$  (Table 2), being consistent with the calculated value and previous structure reports [12, 17, 19, 20]. The hydrogen atom H10A lies on the same

side of the molecule where the C8=O2 carbonyl group is found, in agreement with the <sup>1</sup>H-NMR characterization: its resonance signal appeared at 7.76 ppm, indicating the formation of only the Z-isomer during the synthesis, supporting the results from Table 4. The nitrogen atom from the dimethylamino- group in the *p*-position on the phenyl ring of the benzylidene moiety showed slight  $sp^2$ -hybridization, according to its molecular geometry and bond angles 121.0° (C14-N1-C17), 120.8° (C14-N1-C18), and 116.7° (C17-N1-C18) shown in Table 2. The planes containing the dimethylamino group and the adjacent phenyl group are almost coplanar, their torsion angles: 12.4° and 177.6° for C17-N1-C14-C13 and C18-N1-C14-C13, respectively (Table 2). The N-atom hybridization and the near coplanarity of dimethylamino and adjacent phenyl groups, indicate delocalization of the lone electrons on the

**Table 2** Comparison of geometrical data for compound (I), (Å, °), from X-ray with those calculated from DFT for Z-isomer and Wiberg bond order (WBO) obtained by means of NBO method [18]

	X-ray	DFT	WBO
S1-C1	1.809	1.840	0.986
S1-C2	1.749	1.776	1.075
O2–C8	1.239	1.233	1.690
N1-C14	1.374	1.382	1.151
C9-C10	1.345	1.360	1.688
C12-C13	1.377	1.387	1.497
C1-S1-C2	98.631	98.364	
S1-C1-C9	112.318	112.826	
C14-N1-C17	120.991	119.815	
C14-N1-C18	120.750	119.878	
C17-N1-C18	116.682	118.494	
O2–C8–C7	119.019	119.137	
O2–C8–C9	121.137	121.269	
C1C9C10	124.402	124.965	
C8-C9-C10	118.764	116.619	
C9-C10-C11	129.920	131.221	
C2-S1-C1-C9	54.033	53.308	
S1-C1-C9-C8	- 53.737	-48.707	
S1-C2-C3-C4	- 177.826	178.378	
S1-C2-C7-C6	178.136	- 178.765	
C1C9C10C11	5.038	3.907	
C9-C10-C11-C16	29.728	29.009	
C17-N1-C14-C13	12.361	-7.952	
C18-N1-C14-C13	177.566	-172.390	

nitrogen atom due to a high conjugation of the structure of compound (I), as shown in Fig. 2. This characteristic has also been observed (Fig. 10) in the crystal structure of another compound analogous to compound (I), such as (E)-3-(4-(Dimethylamino)benzylidene)chroman-4-one [17].

Table 2 also includes results from NBO for the isolated molecule of compound (I) [21]: It was found a delocalization pattern, characterized by: (i) delocalization of the electron lone pair from N1 atom toward the

antibonding orbital of the C14 atom, resulting in a slight increase in the N1–C14 bond order; (ii) a shift of the C9=C10 double bond electrons toward the antibonding orbital of the C8–C9 single bond, resulting in a decrease in the C9=C10 bond order, and (iii) the electrons of double bond C2=O8 are shifted to the oxygen atom  $p_{\pi}$ orbital, resulting in a large partial negative charge of – 0.572 a.u. (Table 3) in O2 together with a decrease in its bond order. The electrostatic potential surfaces show the mayor negative charge at the oxygen atom position (red color in Fig. 3).

#### **NBO Atomic Charges**

NBO charge distributions were calculated from the NBO population analysis at the B3LYP/6-31G\*\* level. The computed NBO charge values on each atom of the compound (I) are listed in Table 3.

The carbon atoms (C8 and C14) attached some more electronegative atom exhibited positive charges. The electronegative atoms N1 (-0.430) and O2 (-0.572) exhibited negative charge, but sulfur atom show positive charge. This is due to the great ability of the sulfur atom (S1) to accommodate positive charge (0.296) and have greater dipole polarizability than the carbon atom, since the sulfur atom is more voluminous and its electron cloud is easier to distort [22]. This is the reason why the carbon atom C1 has the highest negative charge (-0.614) among all the carbon atoms in the compound (I), where the inductive effect is more predominant than the resonance effect. After the C1 carbon atom, the carbon atoms of the C17 and C18 methyl group of the dimethylamino moiety are more negative carbon atoms and each has a charge of -0.480 a.u. These carbon atoms attached to the nitrogen atom N1 with charge -0.430 a.u., are those that act as good donor sites of negative charge in the molecule.

Table 4 shows the relative energies (kcal/mole) obtained from the structures optimized for the 3-(4-(Dimethylamino) benzylidene)thiochroman-4-one (Z)- and (E)-isomers. It is observed the energy difference between both isomers in the gas phase is 2.119 kcal/mole, indicating greater stability for



**Fig. 2** Possible resonance structures for compound (I)

Table 3 NB	O atomic charge	e of compound (I)
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Atom	B3LYP/6-31G**	Atom	B3LYP/6-31G**
C1	-0.614	C12	-0.179
C2	-0.172	C13	-0.293
C3	-0.251	C14	0.194
C4	-0.208	C15	-0.292
C5	-0.252	C16	-0.197
C6	-0.175	C17	-0.480
C7	-0.158	C18	-0.480
C8	0.534	N1	-0.430
C9	-0.147	O2	-0.572
C10	-0.133	<b>S</b> 1	0.296
C11	-0.124		



Fig. 3 Electrostatic potential surfaces for compound (I)

 Table 4
 Relative energy (kcal/mole) and dipole moment values for *E*-and *Z*-isomers of (I)

Calculation method	Isomer Z		Isomer E	
	Energy	μ (debyes)	Energy	μ (debyes)
B3LYP/6-31G**	0.000	5.642	2.119	3.729

the (Z)-isomer of compound (I) (geometry of the structure optimized in Fig. 4a), in agreement with the solid state structure determined by X-ray diffraction in the present study. In addition, it has been found in the literature the obtaining of compounds analogous to the (E)-isomer under conditions different from those used in the synthesis in the present work [10, 11].

## **Vibrational Analysis**

The vibrational frequencies of compound (I) were calculated at the B3LYP/6-31G\*\* level of theory with a scale factor of 0.9613 ( $rms_{ov} = 34 \text{ cm}^{-1}$ ) and IR spectrum was

plotted using Gaussview 5.0.8 viewing package. This spectrum is shown in Fig. 5 along with the corresponding experimental spectrum for comparison. The major experimental and calculated frequencies are also summarized in Table 5. There were some deviations in infrared intensities between the experimental data and the calculated data. Any discrepancy noted between the observed and calculated frequencies may be due to two things: one is that the experimental results belong to solid phase whereas theoretical calculations were performed in gaseous phase; and the other is that the calculations were actually done on a single molecule while the experimental values recorded taking into consideration the inter-molecular interactions. The Peaks found in the calculated and the experimental spectrums are important for the presence of the functional groups in compound (I).

The medium peaks in the calculated spectra by the DFT method in compound (I) appeared between 3081 and 2883 cm<sup>-1</sup>. The peak of 3081 cm<sup>-1</sup> corresponds to the stretching of the bond =C-H of the aryl rings of the bicycle thiochroman-4-one and the benzylidene moiety, while in the experimental spectrum this peak appeared at 3050 cm<sup>-1</sup>. The peaks calculated at 3030 and 2891 cm<sup>-1</sup> are due to the stretching symmetric of the C-H bond of the dimethylamino moiety, which are found experimentally at 2990 and 2850 cm<sup>-1</sup>, respectively; and the calculated asymmetric stretching of the C-H bond appears at 2950 and 2883 cm<sup>-1</sup>, while in the experimental spectrum these bands are located at 2900 and 2800 cm<sup>-1</sup>.

The strong peaks in the calculated spectrum of the carbonyl group stretching C=O and the bending C-H, are located at 1664 and 1508 cm<sup>-1</sup>, and in the experimental spectrum at 1650 and 1440 cm<sup>-1</sup>. The remaining peaks (very strong) at 1608 and 1570 cm<sup>-1</sup> correspond to the stretching of the group C=C; 1300 cm<sup>-1</sup> at the N-C stretching and 1380 cm<sup>-1</sup> at the C-H bending in the experimental spectrum. While in the calculated spectrum the peaks of the stretching C=C appears at 1608 and 1566 cm<sup>-1</sup>; stretching N-C to 1344 cm<sup>-1</sup> and the bending C-H to 1420 cm<sup>-1</sup>.

Most of the calculated frequency values had a difference of  $0-50 \text{ cm}^{-1}$  with respect to its experimental value, with the exception of the experimental values of the stretching at 2800 cm<sup>-1</sup> and the bending at 1400 cm<sup>-1</sup> of the C–H bond, whose difference of the calculated values was > 50 cm<sup>-1</sup>, despite having taken into account a correction factor 0.9613 in its frequency values.

#### **Crystal Packing**

The structure of the compound is assembled from the dipole–dipole S–C  $[C2\cdots S1 = 4.4826(38) \text{ Å}]$  interactions of the dimers, as shown in Fig. 6. This interaction



Fig. 4 Optimized geometries of the structures of: a (Z)-3-(4-(Dimethylamino)benzylidene)thiochroman-4-one and b (E)-3-(4-(Dimethylamino) benzylidene)thiochroman-4-one



**Fig. 5** Infrared spectrum of the compound (I); experimental (*above*) and theoretical (*below*)

is supported by the calculated values of charge for the atoms C2(-0.172) and S1(0.296), which are shown in Table 3. Table 4 also shows the values of the total dipole moment of the (Z)-isomer (compound I) and a

Table 5 Assignments of experimental and calculated vibrational scaled frequencies  $(cm^{-1})$  of the compound (I)

Vibrational assignments <sup>a</sup>	Experimental <sup>b</sup>	B3LYP/6-31G**
V = C - H	3050 m	3081
$v_{\rm C-H}^{\rm s}$	2990 m	3030
$v_{C-H}^{as}$	2900 m	2950
$v_{C-H}^{s}$	2850 m	2891
$v_{C-H}^{as}$	2800 m	2883
$v_{\rm C} = 0$	1650 s	1664
$v_{\rm C} = c$	1608 vs	1608
$V_{\rm C} = C$	1570 vs	1566
$\delta_{\rm C-H}$	1440 s	1508
$\delta_{ m C-H}$	1380 vs	1420
V <sub>N-C</sub>	1300 vs	1344

<sup>a</sup> $\nu$  stretching,  $\delta$  bending in plane, *as* asymmetric, *s* symmetric <sup>b</sup>*s* strong, *ms* medium strong, *vs* very strong, *m* medium



Fig. 6 Dipole-dipole interactions S1-C2 of the compound dimers



Fig. 7 Total dipole moments of the dimers of the compound (I)

hypothetical (*E*)-isomer formed during the synthesis. We can see that the (*Z*)-isomer, in addition to a lower energy, the magnitude of its total dipole moment of the calculated molecule (Table 4 and Fig. 7) is always two or three times greater than the (*E*)-isomer, which favors intermolecular interactions. These dimers are connected to each other through dipole–dipole interactions N–C

[C14...N1 = 4.105(43) Å and C14<sup>i</sup>...N1 = 4.038(45) Å] and O–C [C8...O2 = 4.739(43) Å], forming a one dimensional network in the absence of hydrogen bonds (Fig. 8). The values of the atomic charge for these dipoles that are shown in Table 3 and Fig. 8 (pointing with arrows to some atoms where the value of the charge belongs) are: N1(-0.430)–C14(0.194) and O2(-0.572)–C8(0.534). Each of these molecules being joined by the dipolar interactions S1–C2...S1–C2, N1–C14...N1–C14 and O2–C8...O2–C8. The extended arrangement of this compound it is shown in Fig. 9 and consists of an arrangement of dimmer layers through the crystallographic plane ab.

By way of comparison, by exchanging the sulfur atom in compound (I) for an oxygen atom, the molecules are arranged face to face through  $\pi$ - $\pi$  interactions between phenyl rings of the benzylidene group and benzenes adjacent to the pyran-4-one ring (Fig. 10) [17]. There is no centrosymmetric inversion point as in the crystal arrangement of compound (I).



Fig. 8 Dashed lines indicate dipole-dipole interactions between pairs of molecules: S1-C2 (green), N1-C14 (blue) and O2-C8 (red) (Color figure online)



Fig. 9 A view of the two dimensional network of dimers extended in crystallographic plane ab

# Conclusion

Compound (I) is prepared by Claisen–Schmidt condensation reaction with thiochroman-4-one and 4-dimethylaminobenzaldehyde. Slow evaporation solution growth method at room temperature was employed to grow single crystal of good quality for X-ray diffraction. The formation of the compound was also confirmed by spectroscopic analysis. The Wiberg Bond Order analysis determined the delocalization of the pair of solitary electrons of the nitrogen atom in the conjugation of the double bonds of the compound (I). Molecular geometries and vibrational spectrum of the compound was investigated using the DFT method. The calculated geometry of the compound is in good agreement with the X-ray crystallographic data, while the calculated vibrational spectrum compared with the experimental data shown some variations. The energy calculations of the molecular structures and the X-ray diffraction analysis, revealed the formation of the (Z)-isomer of the compound instead of the (E)-isomer. The studies of X-ray diffraction revealed strong intermolecular interactions between dimers of the compound in the absence of hydrogen bonding. These dimers are connected to each other through dipole–dipole interactions S–C, N–C y O–C.



Fig. 10 A view of the two dimensional network of dimers extended in crystallographic plane a for the structures of the compound (E)-3-(4-(Dimetilamino)benciliden)croman-4-ona [17]

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