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ORIGINAL PAPER

Crystal Structure of 3-(4-Methoxy-benzylidene)-isothiochroman-4-one

M. Akkurt · S. Ö. Yıldırım · A. Kerbal · B. Bennani · T. Ben Hadda · Z. H. Chohan · Vickie McKee

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Abstract The title compound, 3-(4-methoxy-benzylidene)-isothiochroman-4-one ($C_{17}H_{14}O_2S$) was prepared from the reaction of isothiochroman-4-one with benzaldehyde in the presence of small amount of HCl. The structure of the synthesised compound was determined by IR, ^{1}H NMR and X-ray crystallography. The structure was solved in monoclinic, space group $P2_1/n$ with $a = 3.9773$ (7) Å, $b = 10.918$ (2) Å, $c = 30.609$ (6) Å, $\beta = 90.615$ (3)°, $V = 1329.1$ (4) Å^3, $Z = 4$ and with $R_{int} = 0.047$. The bicyclic ring of isothiochroman-4-one moiety does not adopt a planar geometry. The molecular conformation is stable via C10–H···O1 and C16–H···S1 intramolecular hydrogen-bonding interactions. These contacts involve molecules in an extended two-dimensional sheet to the *bc* plane.

M. Akkurt (✉) · S. Ö. Yıldırım
Department of Physics, F.A.S., Erciyes University, 38039 Kayseri, Turkey
e-mail: akkurt@erciyes.edu.tr

A. Kerbal · B. Bennani
Laboratoire de Chimie Organique, Faculté des Sciences Dhar El Mehraz, Fes, Morocco

T. B. Hadda
Laboratoire de Chimie des Matériaux, Université Mohammed Premier, Oujda, Morocco

Z. H. Chohan (✉)
Department of Chemistry, Bahauddin Zakariya University, Multan, Pakistan
e-mail: dr.zahidchohan@gmail.com

V. McKee
Department of Chemistry, Loughborough University, Leicestershire LE11 3TU, UK

Keywords Crystal structure · 3-(4-Methoxy-benzylidene)-isothiochroman-4-one · Benzaldehyde · Isothiochroman-4-one

Introduction

Spiro-heterocyclic compounds containing one or two functionalised arms at various positions have emerged as potentially interesting drugs owing to their patented selective antitumoral behaviour against breast-cancer (MCF7-strains) [1], antitubercular agents [2] or anti-HIV agents [3]. These studies showed that spiro-heterocyclic compounds bearing an oxygen or sulfur heteroatom in the 3-position/C=O are highly active not only as anti-tubercular or anti-HIV agents but as potential combined antitubercular/anti-HIV agents [4]. From the general structure–activity relationship, it appears that functionalized side chain(s) characterised by pendant sites such as (O=C–Y–Z), where Y–Z is N=N or O–N, are crucial for bioactivity. The incorporated heteroatom centres S or O on 3-position seem to have critical interactions with the bacterial cell receptors or may be as centre donors in metal complexation. The isothiochroman-4-one, was prepared since a long time [5] by cyclising the chloride 4-phenyl-3-thiabutanoïc acid in nitrobenzene in presence of tri-chloride aluminium. The chloride 4-phenyl-3-thiabutanoïc acid has been cyclised by addition of trichloride aluminium in a mixture of (chloroforme/disulfure-carbone). A group of researcher [6] has improved its yield by cyclising the 4-phenyl-3-thiabutanoïc acid (**3**) by addition of phosphoric anhydride [P_2O_5] on "Hyflosupercelle" in benzene. After this period, another group [7] has cyclised this chloride 4-phenyl-3-thiabutanoïc acid by using the stannic chloride ($SnCl_4$) as catalysor in the disulfure of carbone. In addition the synthesis of the titled

compound containing the sulphur atom at position 3 has been undertaken. In this connection, we recently investigated the synthesis and optimisation of starting expensive precursors of these spiro-heterocycles [8]. In a continuation of our investigations of the precursors synthesis, we describe here the synthesis and structure of 3-(4-methoxy-benzylidene)-isothiochroman-4-one (**6**), the principal precursor of our spiro-anti-HIV drugs.

Results and Discussion

Chemistry

The general protocol of the compound, isothiochroman-4-one (**5**) analogues synthesis consists to realise the intramolecular reaction of Perkin on (o-carboxy)-benzyl-oxyacetic ester or intramolecular reaction of Dieckmann on substituted (*o*-carboxy)-benzyloxythiacetic acid or (*o*-methoxycarbonyl-ester or *o*-ethoxycarbonyl)-benzyloxy-acetic ester or (*o*-methoxycarbonyl or *o*-ethoxycarbonyl)-benzylyhioacetic esters, followed by a decarboxylation [9, 10] as described in (Scheme 1).

The titled compound, 3-(4-methoxy-benzylidene)-isothiochroman-4-one (**6**) has synthesised through number of intermediate reactions. Benzyl chloride reacted with sodium salt of ethyl-thioglycolate (NaS-CH_2-CO2Et) in the presence of ethanol–water solution (50:50) to produce acetic acid of 4-phenyl-3-thiabutanoate of ethyl-ester (**2**). The 4-phenyl-3-thiabutanoïc acid (**3**) was obtained by hydrolysis of 4-phenyl-3-thiabutanoate of ethyl-ester (**2**) in a mixture of concentrated hydrochloric acid and acetic acid. Similarly, 4-phenyl-3-thiabutanoïc acid (**4**) was obtained by the reaction of compound (**3**) with $SOCl_2$. Further, 4-phenyl-3-thiabutanoïc acid (**4**) reacted with toluene in presence of aluminium chloride [6, 7] to give isothiochroman-4-one (**5**) which on reacted with aromatic aldehyde to give title compound (**6**).

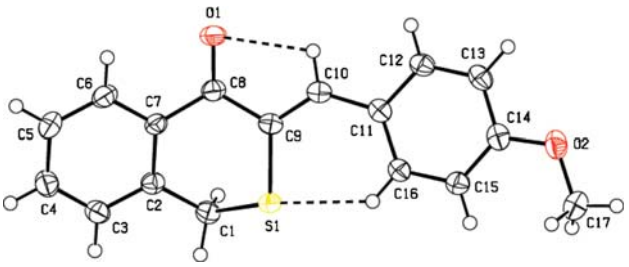
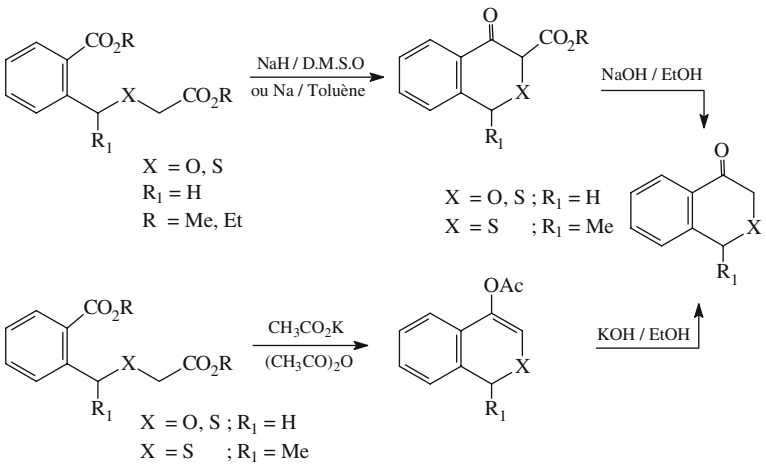


Fig. 1 The molecular structure of (**6**) with the atom-numbering scheme and 50% probability displacement ellipsoids. H atoms have been saved for C8=O1···H10 and C16–H16···S1 possible intramolecular interactions

Crystal Structure

The molecular structure of (**6**) (Fig. 1, Table 1) shows the expected bond lengths and angles [11]. The thiopyran-3-one ring of the isothiochroman-4-one unit are far away to be perfectly planarity [the puckering parameters are $Q_T = 0.620(3)$ Å, $\theta = 177.6$ (4)° and $\varphi = 93$ (8)° [12]. The functionalised groups (C8=O1 and S1–C9) adopts a *Z*-configuration around double bond C9=C10 and O1–C8. On the other hand C9=C10 double bonds are in a non common plane with a torsion angle (O1=C8–C9=C10) of 13.3(4) Å, while the C9–C10–C11–C16 torsion angle is −8.1 (5)°.

The sulfure atom adopts a *cisoidal* conformation with H–C16 atom (Fig. 1). The dihedral angle between the C7/C2/C1 and C1/S1/C9 planes is calculated as 52.63° (24) by using the PARST program [13], while the dihedral angle between the two benzene rings (C2–C7) and (C11–C16) is 34.68 (14)°. In the structure, there is no classic hydrogen bonds, but only weak C10–H···O1 and C16–H···S1 intramolecular interactions, as detailed in Table 2. These contacts involve molecules in an extended two-dimensional sheet parallel to the *bc* plane (Fig. 2).



Scheme 1 General protocol leading to isothiochroman-4-ones and analogues (X = O,S)

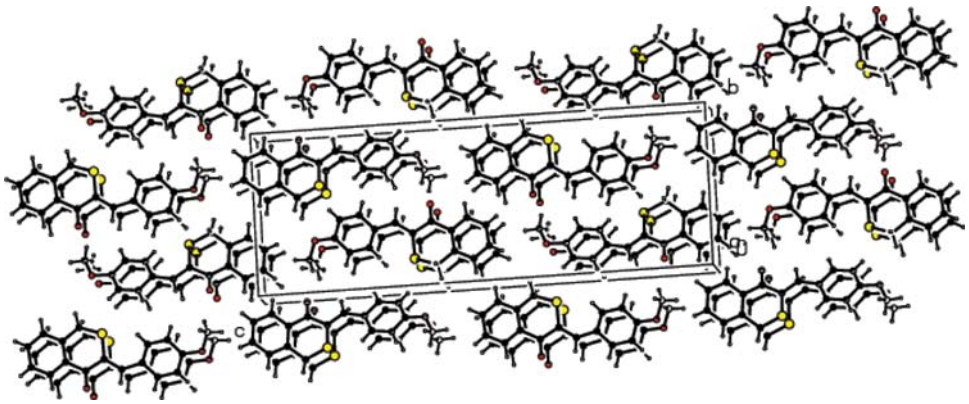


Fig. 2 View of the packing diagram of compound (6) in the unitcell

Table 1 Crystal data and refinement information

Crystal data	
$C_{17}H_{14}O_2S$	$Z = 4$
$M_r = 282.35$	$D_x = 1.411$ Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation
$a = 3.9773$ (7) Å	Cell parameters from 2,891 reflections
$b = 10.918$ (2) Å	$\theta = 2.3$–$25.7°$
$c = 30.609$ (6) Å	$\mu = 0.24$ mm^{-1}
$\beta = 90.615$ (3)°	$T = 150$ (2) K
$V = 1329.1$ (4) Å^3	Lath, yellow
Data collection	
Bruker APEX-II CCD diffractomer	2,643 reflections with $I > 2\sigma(I)$
φ and ω scans	$R_{int} = 0.047$
Absorption correction: none	$\theta_{max} = 28.4°$
12,832 measured reflections	$h = -5 \rightarrow 5$
3,224 independent reflections	$k = -14 \rightarrow 14$
	$l = -40 \rightarrow 40$
Refinement	
Refinement on F^2	H atoms constrained to parent site
$R[F^2 > 2\sigma(F^2)] = 0.071$	Calculated weights $w = 1/[\sigma^2(F_o^2) + (0.0795P)^2 + 2.2377P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.176$	$(\Delta/\sigma)_{max} < 0.0001$
$S = 1.02$	$\Delta\rho_{max} = 0.77$ eÅ^{-1}
3,224 reflections	$\Delta\rho_{min} = -0.33$ eÅ^{-1}
182 parameters	Extinction correction: none

Table 2 Selected geometric parameters (Å, °)

S1–C1	1.811 (3)	C7–C8	1.497 (4)
S1–C9	1.759 (3)	C8–C9	1.493 (4)
O1–C8	1.225 (4)	C9–C10	1.355 (4)
O2–C14	1.368 (4)	C10–C11	1.464 (4)
O2–C17	1.438 (4)	C11–C16	1.400 (4)
C2–C7	1.402 (5)		
C1–S1–C9	99.85 (15)	C7–C8–C9	119.3 (3)
C14–O2–C17	116.7 (2)	S1–C9–C8	119.1 (2)
S1–C1–C2	111.3 (2)	S1–C9–C10	123.4 (2)
C1–C2–C3	121.5 (3)	C8–C9–C10	117.3 (3)
C1–C2–C7	119.7 (3)	C9–C10–C11	131.6 (3)
O1–C8–C7	119.8 (3)	C10–C11–C16	126.0 (3)
O1–C8–C9	120.8 (3)	O2–C14–C13	115.8 (3)
O2–C14–C15	124.8 (3)		
C9–S1–C1–C2	−55.4 (2)	C2–C7–C8–O1	151.8 (3)
C1–S1–C9–C8	28.2 (3)	C2–C7–C8–C9	−30.8 (4)
C1–S1–C9–C10	−157.5 (3)	C6–C7–C8–O1	−27.8 (4)
C17–O2–C14–C13	−179.8 (3)	C6–C7–C8–C9	149.6 (3)
C17–O2–C14–C15	0.5 (4)	O1–C8–C9–S1	−172.0 (2)
S1–C1–C2–C3	−135.0 (3)	O1–C8–C9–C10	13.3 (4)
S1–C1–C2–C7	46.7 (3)	C7–C8–C9–S1	10.7 (4)
C1–C2–C3–C4	−178.3 (3)	C7–C8–C9–C10	−164.0 (3)
C1–C2–C7–C8	−1.0 (4)	S1–C9–C10–C11	0.7 (5)
C8–C9–C10–C11	175.1 (3)	C9–C10–C11–C16	−8.1 (5)
C12–C13–C14–O2	−177.4 (3)	O2–C14–C15–C16	177.2 (3)

Hydrogen-bond parameters (Å, °)

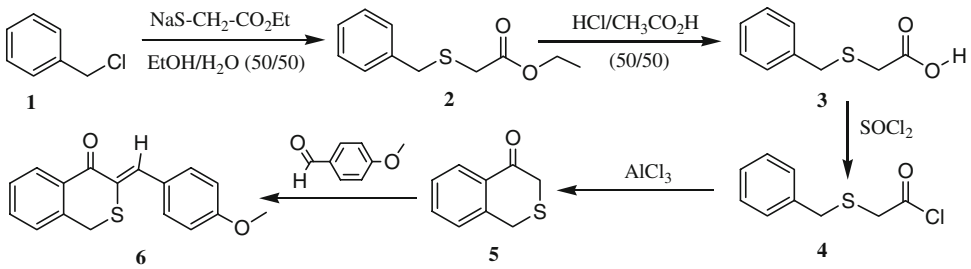
D–H···A	D–H	H···A	D···A	D–H···A
C10–H10···O1	0.93	2.35	2.758(4)	106
C16–H16···S1	0.93	2.47	3.165 (3)	131

Experimental

Synthesis of 3-(4-Methoxy-benzylidene)-isothiochroman-4-one (6)

To a mixture of isothiochroman-4-one (**5**) (40 mmol) and benzaldehyde (40 mmol) were added in little portions 15 mL of chlorohydric acid (HCl) and then the solution is stirred at room temperature for 24 h. A white precipitates were formed. It was filtered and then purified by simple crystallisation in ethanol. The desired compound (**6**) was separated from ethanol as analytically pure uncoloured crystals (Scheme 2).

Scheme 2 Synthesis of 3-(4-methoxy-benzylidene)-isothiochroman-4-one (**6**)



Transparent crystals. Yield 87%. M.p. = 93–95 °C. IR (nujol, v cm^{-1}): 1,647 (C=O), 1,570 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.1 (s, 1H, C10–H), 6.1–8.0 (m, 8H, 2 Ph), 3.9 (s, 2H, $SC\underline{H}_2$), 3.8 (s, 3H, OCH_3).

The 4-phenyl-3-thiabutanoate-ethyle (**2**), 4-phenyl-3-thiabutanoic acid (**3**), chloride 4-phenyl-3-thiabutanoic acid (**4**) and isothiochroman-4-one (**5**) have been prepared as described in literature.

4-Phenyl-3-Thiabutanoate Ethyle (2)

Yield = 85%. Eb = 114 °C. IR (nujol) v(cm^{-1}): 1,720 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.23 (t, 3H, $C\underline{H}_3$–CH_2, J = 7 Hz); 3.02 (s, 2H, 2H^2); 3.80 (s, 2H, 2H^4); 4.10 (q, 2H, CH_3–$C\underline{H}_2$, J = 7 Hz); 7.25 (m, 5H, ph).

4-Phenyl-3-Thiabutanoic Acid (3)

Yield = 42%; mp = 64 °C. IR (KBr): v(cm^{-1}): 2,300–3,300 (OH); 1,695 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.15 (s, 2H, H^2); 3.85 (s, 2H, 2H^4); 10.20 (s, 1H, OH); 7.35 (m, 5H, Ph).

Chloride 4-Phenyl-3-Thiabutanoic Acid (4)

Yield = 80%. Eb = 125 °C. IR (nujol) v(cm^{-1}): 1,790 (C=O). ^{1}H NMR ($CDCl_3$) δ(ppm): 3.45 (s, 2H, 2H^2); 3.75 (s, 2H, 2H^4); 7.25 (m, 5H, Ph).

Isothiochroman-4-One (5)

White crystals. Yield = 50% . Eb = 138 °C. F = 60 °C. IR (KBr): v(cm^{-1}): 1,670 (C=O). ^{1}H NMR ($CDCl_3$): 3.55 (s, 2H, 2H^3); 3.95 (s, 2H, 2 H^1); 7.15–7.55 (m, 3H, Ph); 8.10 (m, 1H).

H atoms were geometrically located in calculated positions and treated as riding on their parent atoms, with C–H = 0.93–0.97 Å, and with U_{iso}(H) = 1.2U_{eq}(C) and U_{iso}(H) = 1.5U_{eq}(C) for methyl group.

Data collection: APEX2 [14]. Cell refinement: APEX2. Data reduction: SAINT. Program(s) used to solve structure: SIR97 [15]. Program(s) used to refine structure: SHELXL97 [16]. Molecular graphics: ORTEP-3 for Windows [17]. Software used to prepare material for publication: WinGX [18].

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References

1. Bennani B, Kerbal A, Larbi NB, Hadda TB (2004) Synthesis and application of spiro-isoxazolines as new anti-tubercular agents. Moroccan Patent, Casablanca, N 2769
2. Bennani B, Kerbal A, Larbi NB, Hadda TB (2004) Synthesis and application of isothiochromeno[3,4-e][1,2]oxazines (TCO) as new anti-tumoral agents. Moroccan Patent, Casablanca, N 2771
3. Bennani B, Kerbal A, Larbi NB, Hadda TB (2004) Synthesis and application of some spiro-isoxazolines as new anti-HIV agents. Moroccan Patent, Casablanca, N 2770
4. Bennani B, Kerbal A, Daoudi M, Baba BF, Houari GA, Jalbout AF, Mimouni M, Benazza M, Demailly G, Akkurt M, Yıldırım SÖ, Hadda TB (2007) ARKIVOC xvi:19–40
5. Lesser R, Mehrlander A (1923) Ber 56:1642–1648
6. Brown JV, Weissbach K (1929) Chem Ber 62:2416–2425
7. Gagnant P, Gagnant D (1959) Bull Soc Chim Fr, 1998
8. Houari GA, Kerbal A, El Bali B, Bolte M (2005) Acta Cryst E61:o3330–o3333
9. Thibault J (1971) Ann Chim (Paris) 6:381
10. Pulman DA, Whiting DA (1973) J Chem Soc Perkin Trans 1 1(4):410–418
11. Allen FH (2002) Acta Cryst B58:380–388
12. Cremer D, Pople JA (1975) J Am Chem Soc 97:1354–1358
13. Nardelli M (1983) Comput Chem 7:95–98
14. Bruker (2005) APEX2 (Version 2.1) and SAINT (Version 7.23A). Bruker AXS Inc., Madison
15. Altomare A, Burla MC, Camalli M, Cascarano GL, Giacovazzo C, Guagliardi A, Moliterni AGG, Polidori G, Spagna R (1999) J Appl Cryst 32:115–119
16. Sheldrick GM (2008) Acta Cryst 64:112–122
17. Farrugia LJ (1997) J Appl Cryst 30:565
18. Farrugia LJ (1999) J Appl Cryst 32:837–838