



Preparation, Crystal Structure and Molecular Structure Studies and Hirshfeld Surface Analysis of (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one

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Abstract: Knoevenagel condensation of 2-acetylthiophene and 4-methoxybenzaldehyde in the presence of potassium hydroxide in methyl alcohol at room temperature afforded (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one. The synthesised compound was characterized by ¹H NMR, Mass spectral and X-ray diffraction studies. The title molecule (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one is crystallized in the monoclinic crystal system with the space group P2₁. The unit cell axes along *a*, *b* and *c* measure 4.149 (6) Å, 10.038 (1) Å and 14.552 (2) Å respectively and the angle between axis *a* and *c* was 91.9 (2)°. The number of formula units *Z* in the unit cell was 2. The crystal and molecular structure of the title compound is stabilized by C—H ...O hydrogen bond interactions. The Hirshfeld surface analysis was carried out to make it evident the presence of C—H ...O hydrogen bond interactions and to find the contributions of various inter molecular close contacts which stabilize the crystal lattice structure.

Keywords: Condensation; Chalcone; Methanol; Packing; Hirshfeld surface.

1. Introduction

Design and developing a procedure for the transformation of simple molecules into bioactive molecules with different functionalities is a worthwhile contribution in organic synthesis. Among the simple molecules, α , β -unsaturated carbonyl compounds were proven as versatile intermediates in organic synthesis for the construction of wide range of bioactive molecules. The Claisen-Schmidt reaction was commonly employed route for preparation of α , β -unsaturated ketones; which involves the reaction of aromatic aldehydes with aromatic ketones in the presence of bases [1]. Alternatively, α , β -unsaturated carbonyl compounds were synthesised usually by Knoevenagel condensation reaction of aromatic aldehydes with active methylene compounds in the presence of bases [2, 3]. For instance, condensation of the *p*-chlorobenzaldehyde and ethyl acetoacetate in benzene with a catalytic amount of piperidine and trifluoro acetic acid offers chlorobenzylidene chalcones, which acts as good Michael-addition acceptors and can be used directly in the Diels-Alder reaction and are of wide synthetic utilities in pharmaceutical industries [4]. An enzyme Lipase lipoprotein (LPL) isolated from *A. niger* proved to be the effective catalyst for the Knoevenagel condensation of aromatic aldehydes and active methylene compounds in a green protocol [5]. The stereochemical assignment for the α , β -unsaturated ketones were made on the basis of DPGSE-NOE (Double Pulse Field Gradient Spin Echo NOE) experiments [6].

α , β -Unsaturated ketones were extensively used as building blocks in the synthesis of bioactive molecules. For instance, the reaction of α -benzotriazolyl α , β -unsaturated ketones with hydroxylamine and monosubstituted hydrazines produced 2,5-disubstituted isoxazoles and 1,3,5-triaryl-4-alkylpyrazolines with high regioselectivity [7]. Analogues of α , β -unsaturated ketones have been extensively studied for their biological activities and were known to exhibit anti-inflammatory [8], antifungal, antibacterial [9, 10], antileishmanial, antiparasitic [11], antitubercular [12] and antioxidant activity [13]. These classes of simple molecules were used as precursors in the synthesis of pharmacologically important molecules such as pyrazoles [14-16], isoxazolines [17, 18], thiazoles [19], benzothiazepines [20, 21] etc.

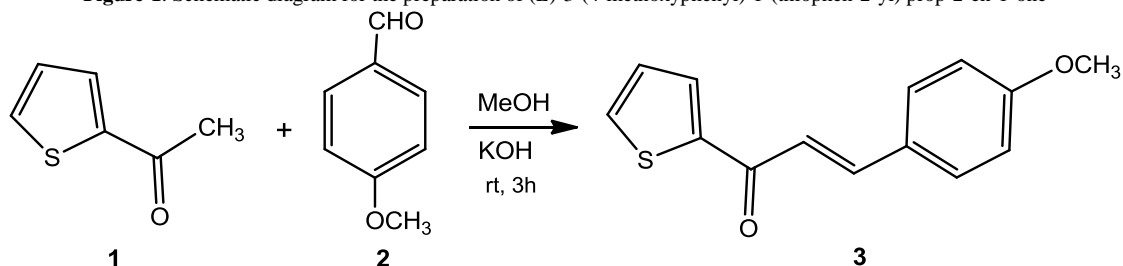
In view of wide applications associated with α , β -unsaturated carbonyl compounds, we herein report the preparation, crystal growth, spectral analysis and single crystal X-ray diffraction studies of (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one.

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2. Materials and Methods

To the solution of 4-methoxybenzaldehyde, **2** (0.01 mol) and 2-acetylthiophene, **1** (0.01 mol) in methyl alcohol (20 mL), powdered KOH (0.01 mol) was added; the mixture was stirred at room temperature for 3 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water and kept in the refrigerator for overnight. The solid separated was filtered, washed with ice cold water and crystallized from ethyl acetate to obtain (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one, **3** as light yellow rectangular block like crystals in 85% yield, m.p. 71-73 °C (ref. 70-72°C) [22]. The schematic diagram of the reaction is depicted in Figure 1.

Figure-1. Schematic diagram for the preparation of (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one



2.1. Spectral Analysis

¹H NMR spectra was recorded on Agilent-NMR 400 MHz spectrometer in CDCl₃. The chemical shifts are expressed in δ ppm. Mass spectra were obtained on Mass Lynx SCN781 spectrometer TOF mode. ¹H NMR (CDCl₃): δ 3.85 (s, 3H, OCH₃), 6.69 (d, 1H, CH=), 7.01-7.12 (dd, 2H, Ar-H), 7.42-7.56 (dd, 2H, Ar-H), 7.62 (d, 1H, =CH), 7.98-8.14 (m, 3H, thiophene ring=H). MS (m/z) for C₁₄H₁₂O₂S: 244 (M⁺, 100). In ¹H NMR spectra, title compound showed a singlet at δ 3.85 ppm. for OCH₃ protons, due to para substitution effect, four aromatic protons of methoxy substituted phenyl ring absorbed as doublets of doublet for two protons each at δ 7.01-7.12 and 7.42-7.56 ppm. Two doublets for one proton each absorbed at δ 6.69 and 7.62 ppm were assigned to alkenyl CH= and =CH protons. In Mass spectra, compound showed M⁺ peak at m/e 244 corresponding to molecular mass as base peak.

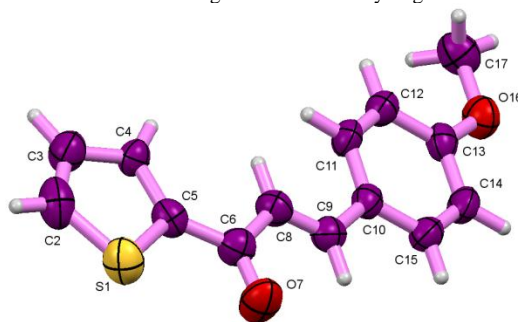
2.2. Structure Determination

A light yellow rectangular block shaped single crystal of dimension 0.27×0.32×0.37 mm of the title compound was selected and X-ray intensity were collected with χ fixed at 54° and φ, from 0° to 360°, scan width at 0.5°, exposure time of 3 s and the sample to detector distance of 50.0 mm at a temperature 293 K on Rigaku XtaLAB Mini X-ray diffractometer operating at 50 kV and 12 mA with MoK_α radiation of wavelength λ=0.71073 Å. A complete data set was processed by CRYSTAL CLEAR [23]. The structure was solved by direct methods and refined by full-matrix least squares method on F² using SHELX [24]. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residual is saturated to 0.0524. The geometrical calculations were carried out using PLATON [25]. The molecular and packing diagrams were generated using MERCURY [26].

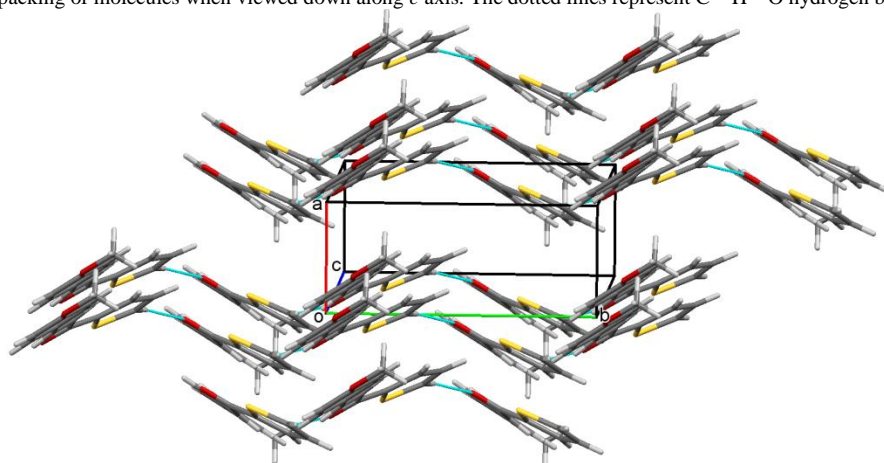
3. Results and Discussion

The title compound, (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one is crystallized in the monoclinic crystal system with the space group P2₁ and with unit cell parameters, *a* = 4.149 (6) Å, *b* = 10.038 (1) Å, *c* = 14.552 (2) Å; β = 91.9 (2)° and *V* = 605.7 (1) Å³. The ORTEP of the molecule with displacement ellipsoids drawn at 50 % probability level is shown in Figure 2.

Figure-2. The ORTEP of the molecule with numbering scheme for non hydrogen atoms drawn at 50% probability level.



The crystal data and the structure refinement details are given in Table 1. The bond lengths, bond angles and torsion angles are given in Table 2. The molecules are packed layer-by-layer to form a three dimensional supra molecular network shown in Figure 3.

Figure-3. The packing of molecules when viewed down along *c* axis. The dotted lines represent C—H···O hydrogen bond interactions.**Table-1.** Crystal structure data and structure refinement details.

Empirical formula	$C_{14}H_{12}O_2S_1$
Formula weight	244.3 g mol ⁻¹
Temperature	293 K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2 ₁
Unit cell dimensions	$a = 4.149 (6) \text{ \AA}$ $b = 10.038 (2) \text{ \AA}$ $c = 14.552 (2) \text{ \AA}$ $\beta = 91.9 (2)^\circ$
Volume	605.7 (1) Å ³
Z, calculated density	2, 1.340 Mg/m ³
Absorption coefficient	0.253 mm ⁻¹
F_{000}	256
Crystal size	0.27 × 0.32 × 0.37 mm
Theta ranges for data collection	3.5° to 27.5°
Limiting indices	$-4 \leq h \leq 5, -12 \leq k \leq 7, -12 \leq l \leq 18$
Absorption correction	Multi-scan, $T_{\min} = 0.912, T_{\max} = 0.935$
Reflections collected / unique	2082 / 1901 ($R_{\text{int}} = 0.031$)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1901 / 0 / 155
Goodness-of-fit on F^2	1.08
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0524, wR2 = 0.1480$
R indices (all data)	$R1 = 0.0626, wR2 = 0.1592$
Largest diff. peak and hole	0.35 and -0.24 e. Å ⁻³

Table-2. Bond lengths, bond angles and torsion angles (Å, °).

S1—C2	1.687 (6)	C9—C10	1.465 (5)
S1—C5	1.708 (4)	C10—C11	1.392 (6)
C2—C3	1.353 (7)	C10—C15	1.397 (5)
C3—C4	1.452 (6)	C11—C12	1.363 (5)
C4—C5	1.423 (6)	C12—C13	1.409 (5)
C5—C6	1.457 (6)	C13—O16	1.352 (5)
C6—O7	1.215 (5)	C14—C15	1.369 (6)
C6—C8	1.495 (5)	O16—C17	1.429 (6)
C8—C9	1.311 (6)		
C2—S1—C5	92.5 (2)	C11—C10—C15	117.0 (3)
C3—C2—S1	113.3 (3)	C11—C10—C9	122.8 (3)
C2—C3—C4	113.2 (4)	C15—C10—C9	120.2 (4)
C5—C4—C3	109.1 (3)	C12—C11—C10	122.5 (3)
C4—C5—C6	128.7 (3)	C11—C12—C13	119.6 (4)
C4—C5—S1	112.0 (3)	O16—C13—C14	116.9 (3)
C6—C5—S1	119.3 (3)	O16—C13—C12	124.3 (4)

O7—C6—C5	122.2 (4)	C14—C13—C12	118.8 (4)
O7—C6—C8	120.8 (4)	C15—C14—C13	120.4 (4)
C5—C6—C8	116.9 (4)	C14—C15—C10	121.7 (4)
C9—C8—C6	122.7 (4)	C13—O16—C17	118.1 (3)
C8—C9—C10	126.6 (4)		
C5—S1—C2—C3	0.0 (4)	C8—C9—C10—C11	-4.4 (6)
S1—C2—C3—C4	-0.6 (5)	C8—C9—C10—C15	177.2 (4)
C2—C3—C4—C5	0.9 (5)	C15—C10—C11—C12	0.5 (5)
C3—C4—C5—C6	176.7 (4)	C9—C10—C11—C12	-178.0 (3)
C3—C4—C5—S1	-0.9 (4)	C10—C11—C12—C13	-0.9 (5)
C2—S1—C5—C4	0.5 (3)	C11—C12—C13—O16	-179.2 (3)
C2—S1—C5—C6	-177.3 (3)	C11—C12—C13—C14	0.1 (5)
C4—C5—C6—O7	-177.2 (4)	O16—C13—C14—C15	-179.5 (3)
S1—C5—C6—O7	0.2 (5)	C12—C13—C14—C15	1.3 (5)
C4—C5—C6—C8	1.1 (6)	C13—C14—C15—C10	-1.8 (6)
S1—C5—C6—C8	178.5 (3)	C11—C10—C15—C14	0.9 (5)
O7—C6—C8—C9	9.4 (6)	C9—C10—C15—C14	179.4 (4)
C5—C6—C8—C9	-168.9 (4)	C14—C13—O16—C17	178.7 (3)
C6—C8—C9—C10	178.2 (3)	C12—C13—O16—C17	-2.1 (5)

In a molecule, (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one, a torsion angle of $-168.9 (4)^\circ$ about C5—C6—C8—C9 indicates that the segment C8—C9 is in a *-Anti-Periplanar* conformation with the mean plane described by the thiophene ring S1/C2/C3/C4/C5. The segment O7—C6 is in *+Syn-Periplanar* conformation with respect to the plane described by the atoms C8→C15/O16/C17 as indicated by the dihedral angle $9.5 (6)^\circ$. A dihedral angle of $9.42 (2)^\circ$ between the mean plane of the thiophene ring and the mean plane of the 4-methoxyphenyl ring shows that the 4-methoxyphenyl ring lies in the axial position with the thiophene ring.

The molecules also exhibit $Cg \cdots Cg$ interaction; $Cg2 \cdots Cg2$ ($Cg2$ is the centroid of the ring C10→C15) with a $Cg—Cg$ distance of $4.149 (6) \text{ \AA}$, β and γ being 33.4° , a perpendicular distance of $Cg2$ on ring C10→C15 of the molecule of the adjacent layer and a perpendicular distance of $Cg2$ on ring C10→C15 of the parent molecule being $+3.4653 (2) \text{ \AA}$ [$-1+x,y,z$] and $-3.4653 (2) \text{ \AA}$ [$1+x,y,z$], and slippage, 2.057 \AA . The crystal structure is stabilized by the C—H \cdots O intermolecular hydrogen bond interactions as listed in Table 3. The molecular structure is stabilized by the C—H \cdots O intramolecular interactions forming a five membered ring C6/C8/C9/H9/O7.

Table-3. Hydrogen bond geometry (\AA , $^\circ$).

$D—H \cdots A$	$D—H$	$H \cdots A$	$D \cdots A$	$D—H \cdots A$	Symmetry codes
C2—H2 \cdots O7	0.93	2.60	3.506	166	$-x, \frac{1}{2}+y, 1-z$
C17—H17A \cdots O7	0.96	2.67	3.587	155	$-x, \frac{1}{2}+y, -z$
C9—H9 \cdots O7	0.93	2.52	2.833	100	

The Hirshfeld surface analysis [27, 28] was carried in order to visualize the intercontacts in the molecular structure using *CRYSTAL EXPLORER* [29]. The Hirshfeld surface volume and surface area were 296.28 \AA^3 and 286.56 \AA^2 respectively. The Hirshfeld surface for the title molecule shown in Figure 4 and Figure 5 shows the Hirshfeld surface of the molecule in a 3D crystal structure of the title molecule.

Figure-4. d_{norm} mapped on the Hirshfeld surface for visualizing the intercontacts of the molecule.

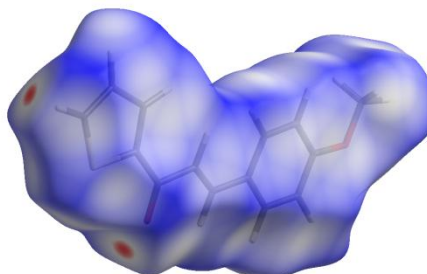
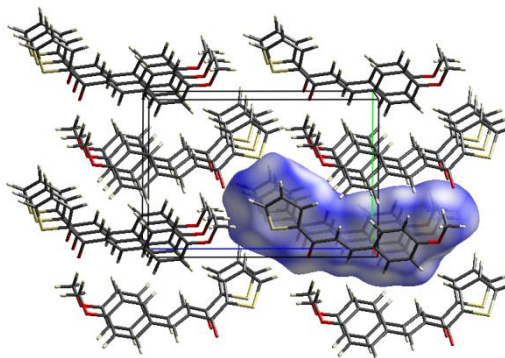
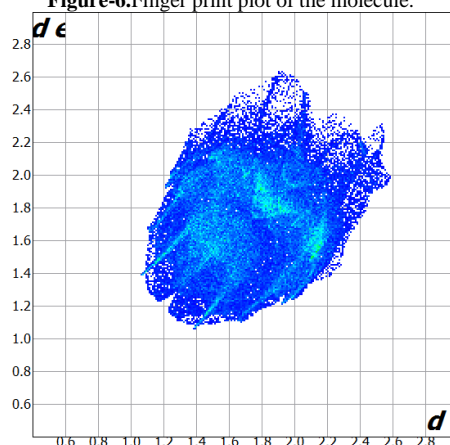


Figure-5. Hirshfeld surface of the molecule in a 3D crystal structure.

The hydrogen bond interactions were visualized with the help of dark red spots on the Hirshfeld surface, as a result of hydrogen bond acceptors C2—H2...O7 and C17—H17A...O7. The combination of d_e and d_i in the form of two-dimensional fingerprint plot [30] gives the summary of intermolecular contacts in the crystal lattice. The fingerprint plot for the title molecule is shown in Figure 6.

Figure-6. Finger print plot of the molecule.

The C...H intercontacts appear as a pair of wider and slightly blunt spikes of light sky-blue colour in the region $1.10 \text{ \AA} < (d_e + d_i) < 1.68 \text{ \AA}$ and S...H inter contacts as a pair of very sharp but wider spikes in the range $1.20 \text{ \AA} < (d_e + d_i) < 1.92 \text{ \AA}$ of the full fingerprint plots. The H...H inter contacts appear as a pair of close blunt spikes of light sky-blue colour in the region $1.07 \text{ \AA} < (d_e + d_i) < 1.27 \text{ \AA}$ and O...H inter contacts as a pair of very sharp spikes in the range $1.04 \text{ \AA} < (d_e + d_i) < 1.39 \text{ \AA}$ of the full fingerprint plots. The fingerprint plots can be separated to highlight the inter contacts of a particular pair of atoms. The contributions of C...H (24 %), O...H(18 %), H...H (39 %), S...H (9 %), C...C(4 %), S...C(3 %),C...O(2 %) intercontacts to the Hirshfeld surface.

4. Conclusions

(*E*)-3-(4-Methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one was synthesized by Knoevenagel condensation reaction of 2-acetylthiophene and 4-methoxybenzaldehyde in the presence of potassium hydroxide in methyl alcohol at room temperature conditions. The title molecule is crystallized in the monoclinic crystal system with the space group P2₁. The molecules also exhibit Cg...Cg interaction and the crystal structure is stabilized by the C—H...O intermolecular hydrogen bond interactions. The hydrogen bond interactions were visualized with the help of dark red spots on the Hirshfeld surface as a result of hydrogen bond acceptors C—H...O. The contributions of C...H (24 %), O...H (18 %), H...H (39 %), S...H (9 %), C...C (4 %), S...C(3 %),C...O(2 %) intercontacts to the Hirshfeld surface.

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