Journal of Structural Chemistry. Vol. 59, No. 6, pp. 1440-1445, 2018.
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STRUCTURAL CHARACTERIZATION OF A NEW CHALCONE COMPOUND CONTAINING A THIOPHENE MOIETY: (*E*)-3-(5-BROMOTHIOPHEN-2-YL)-1-(2,5-DICHLOROTHIOPHEN-3-YL)-2-PROPEN-1-ONE

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The crystal structure of the new chalcone derivative (*E*)-3-(5-bromothiophen-2-yl)-1-(2,5-dichlorothiophen-3-yl)-2-propen-1-one is synthesized and structurally characterized by spectroscopic IR, NMR, and HRMS techniques. Its crystal and molecular structure is determined from the single crystal X-ray diffractionstudy. This compound crystallizes in the monoclinic system and space group *P*21/*n* (N 19). The crystal packing is governed by C---H···O non-conventional hydrogen bond-type intermolecular interactions, forming extended zigzag chains related by 21 screw axes running along the [010] direction, with graph-set C(8). These hydrogen bonds contribute to the stabilization of the crystal structure that packs with an efficiency of 71.4%.

DOI: 10.1134/S0022476618060276

Keywords: synthesis, chalcones, thiophene, crystal structure, hydrogen bond patterns.

INTRODUCTION

Chalcones (1,3-diaryl-2-propen-1-ones) are a class of compounds consisting of two aryl rings linked by an α,β-unsaturated ketone moiety. Chalcones represent an essential group of natural as well as synthetic products and some of them possess a wide range of pharmacological activities.

Heterocyclic chalcone derivatives show interesting and important properties against many of human diseases such as anti-AIDS agents [1], anti-malarial [2], anti-inflammatory [3], anti-leishmanial [4], anti-oxidant [5], anti-cancer [6], and anti-microbial [7].

These interesting compounds could be synthesized by several methods based on the formation of carbon-carbon bonds. Claisen-Schmidt condensation has been used by many groups as a method for the synthesis of chalcone in the presence of an aqueous alkaline base [8]. Other methods could also be used, including Friedel-Crafts acylation [9], the Suzuki coupling reaction [10], microwave irradiation [11], ultrasound irradiation [12], and the grinding technique [13].

In addition, chalcones have been used as an important intermediate compound in the synthesis of five- and six-member rings [14] and as an intermediate in the biosynthesis of flavonoids [15].

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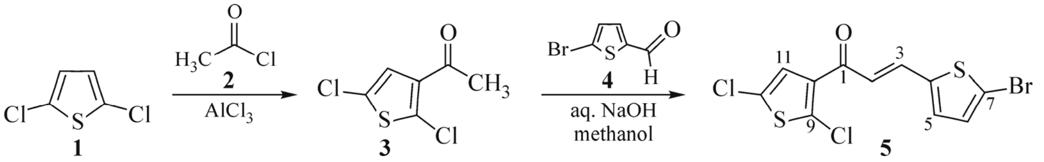
In this work we report the synthesis, spectroscopic characterization, and crystal structure of a new chalcone derivative compound containing two thiophene rings, (*E*)-3-(5-bromo thiophen-2-yl)-1-(2,5-dichlorothiophen-3-yl)-2-propen-1-one, among a series of chalcone thiophene derivatives as potential antimicrobial and anticancer agents [16].

EXPERIMENTAL

Synthesis. The title compound was synthesized by the Claisen-Schmidt condensation method [8] (Scheme 1) using a methodology previously reported [16]. A solution of 2,5-dichlorothiophene (**1**) (100 mmol), acetyl chloride (**2**) (10 ml), and carbon disulfide (10 ml) were mixed. Anhydrousaluminum chloride was slowly addedto the mixture during 15 min. The reaction mixture was stirred at room temperature for overnight, and then cooled and poured into ice water. The carbon disulfide layer was separated and washed three times with water and the solvent was removed to give solid 3-acetyl-2,5-dichlorothiophene product (**3**). Yield 76.7%; m.p. 38-40 °C.

A mixture of **3** (0.03 mol) with 5-bromo-2-thiophenecarboxaldehyde (**4**) (0.03 mmol) was dissolved in methanol (25ml). Aqueous sodium hydroxide (15 ml) was added dropwise and the resulting mixture was stirred overnight at room temperature. The precipitate was collected, dried, and purified by recrystallization from ethanol to give thiophene chalcone (*E*)-3-(5-bromothiophen-2-yl)-1-(2,5-dichlorothiophen-3-yl)-2-propen-1-one (**5**). Yellow needle-like crystals of **5** suitable for the X-ray diffraction analysis were grown by slow evaporation in an ethanol solution. Yield: 83.6%; m.p. 100-102 °C.



Scheme 1. Synthesis of (*E*)-3-(5-bromothiophen-2-yl)-1-(2,5-dichlorothiophen-3-yl)-2-propen-1-one 5.

FT–IR, NMR, and HRMS analyses. Melting points were measured on a Leica Gallen III Kofler micro melting points apparatus. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BrukerAvance II spectrometer using deuterated DMSO and $CDCl_3$ as solvents. Mass spectra were obtained from NUS Mass Spectrometry Service, Singapore.

(**3**) IR ν_{max}, cm^{-1}: 3102 (C–H *sp*^{2}), 3003 (C–H *sp*^{3}), 1659 (C=O); ^{1}H–NMR (DMSO): δ 2.50 (3H, s) and δ 7.53 (1H, s).

(**5**) IR ν_{max}, cm^{-1}: 3078 (Ar–H), 1644 (C=O), 1579, 1512 (Ar–C=C), C–Cl (1020); ^{1}H NMR ($CDCl_3$): δ 7.07(1H, d, *J* = 4 Hz, H-5), δ 7.08 (1H, d, *J* = 15.2 Hz, H-2), δ 7.12 (1H, d, *J* = 4 Hz, H-6), δ 7.19 (1H, s, H-11), δ 7.76 (1H, d, *J* = 15.2 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 117.20 (C-7), δ 122.56 (C-5), δ 127.08 (C-11), δ 127.12 (C-8), δ 131.28 (C-9), δ 131.49 (C-2), δ 132.86 (C-6), δ 136.61 (C-3), δ 137.60 (C-10), δ 141.61 (C-4), δ 182.84 (C-1; Found (HRMS–ESI): 388.8247 [M+Na]$^+$ and 389.8280 [M+H+Na]$^+$, ($C_{11}H_5BrCl_2OS_2$ requires, 388.8240 and 389.8318).

The chemical structure of **5** was determined using ^{1}H NMR,^{13}C NMR, andATR-FTIR. For chalcone **5**, H-2 and H-3 showed a doublet peak which has a big coupling constant of 15.2 Hz. Protons at 5 and 6 carbon atoms also gave a nice doublet with a small coupling constant of 4.0 Hz. Meanwhile, due to no neighboring proton at H-11, it appeared as a singlet peak at δ7.19. The structure of the product was confirmed from the ^{13}C NMR spectra where the carbon atom belonging to the carbonyl group (C=O) gave rise to peaks in the most downfield region of the spectrum at δ182.84. It also showed the presence of eight aromatic carbon atoms that suit the proposed structure of chalcone **5**. The presence of the product was also proven using ATR–FTIR spectroscopy where Ar–H, C=O and C=C aromatic absorption bands at 3078 cm^{-1}, 1644 cm^{-1}, and 1512 cm^{-1} respectively were observed. The ATR-FTIR spectrum of chalcone **5** also showed the presence of the C–Cl stretching vibration in the region of 1020 cm^{-1} indicating the presence of a chlorine atom in the compound.

Single crystal X-ray crystallography. A colorless rectangular crystal (0.07 mm, 0.10 mm, 0.32 mm) was used for data collection. Diffraction data were collected at 295(2) K by the ω-scan technique on a Rigaku Pilatus 200 K diffractometer with MoK_α radiation ($\lambda = 0.71073$ Å). The data were corrected for the Lorentzpolarization and absorption effects [17]. The structure was solved by direct methods using the SHELXS program [18] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [19]. All H atoms were placed at the calculated positions and treated using the riding model, with C–H distances being 0.97-0.98 Å. The U_{iso}(H) parameters were fixed at $1.2U_{\text{eq}}$(C). Table 1 summarizes the crystal data, intensity data collection, and refinement details for the title compound.

CCDC-1447773 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

All spectral data (IR, NMR, and HRMS) obtained were consistent with the structure assigned and confirmed the molecular skeleton. The title compound crystallizes in the centrosymmetric space group $P2_1/n$. Fig. 1 shows the molecular structure and the atom labeling scheme of **5** generated using the Diamond program [20]. All geometrical calculations were made using the Platon program [21]. Selected bond distances, bond angles and torsion angles are presented in Table 2.

Title compound **5** crystallizes with one molecule in the asymmetric unit, in which the structure shows two thiophene rings linked by a prop-2-en-1-one group. The molecule exists in the *E* configuration with respect to the central prop-en-one group defined by the C5–C6–C7–C8 torsion angle of –179.8(4)°. It should be noted that both *cis* and *trans* isomeric forms have been observed in 1,3-diarylprop-2-en-1-ones, but the *trans* isomer is thermodynamically more stable [22].

A search of the Cambridge Structural Database (CSD, version 5.37, May, 2016) [23] revealed four related structures with 2,5-dichlorothiophene fragments and 14 entries with 5-bromo-2-thiophene fragments. All bond distances and angles are in agreement with the experimental average values found for similar structures, as in 3-acetyl-2,5-dichlorothiophene (KUYXEI) [24], (*E*)-1-(2,5-dichloro-3-thienyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (KUYXAE) [25], (*E*)-1-(2,5-dichloro-3-thienyl)-3-[4-(dimethyl amino)phenyl]prop-2-en-1-one (NUQKUG) [26], and (2*E*)-1-(2,5-dichloro-3-thienyl)-3-(6-methoxy-2-naphthyl)prop-2-en-1-one (QUZNEF) [27].

The molecule of **5** is essentially planar with maximum deviations of 0.002(4) Å in C2 and –0.0031(4) Å in C1, 0.001(4) Å in C8 and –0.002(4) Å in C9 for the thiophene rings. The two ring planes of the thiophene groups make a dihedral angle of 1.6(2)°.

TABLE 1. Crystal Data, Data Collection, and Structure Refinement

Chemical formula	$C_{11}H_5BrCl_2OS_2$	CCDC	1447773
Formula weight	368.08	Radiation (MoK_α), Å	$\lambda = 0.71073$
Crystal system	Monoclinic	θ range, deg.	3.0-27.6
Space group	$P2_1/n$	*hkl* range	–4, 4; –17, 17; –30, 30
a, Å	4.0056(2)	Reflections	11886
b, Å	13.4966(9)	Unique	2836
c, Å	23.418(2)	R_{int}	0.038
β, deg.	94.285(6)	With $I > 2\sigma(I)$	2134
V, Å^3	1262.5(1)	Refinement method	Full-matrix least-squares on F^2
Z	4	Number of parameters	154
d_x, g/cm^3	1.323	$R(F^2)$ $[I > 2\sigma(I)]$	0.0436
F(000)	200	$wR(F^2)$ $[I > 2\sigma(I)]$	0.1145
μ, mm^{-1}	0.094	Goodness of fit on F^2	1.0
Crystal size, mm	0.07×0.10×0.32	Max / min Δρ, e/Å^3	0.77 / –0.53

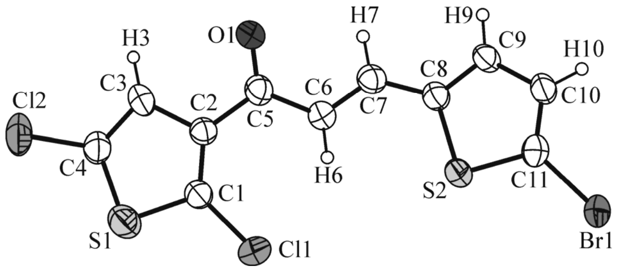


Fig. 1. Molecular structure of **5** showing the atom numbering scheme. Displacement ellipsoids are drawn at a 50% probability level. H atoms are shown as spheres of arbitrary radii.

TABLE 2. Selected geometrical parameters (Å, deg.) for **5**

Br1–C11	1.867(4)	O1–C5	1.215(6)
S1–C1	1.697(4)	S1–C4	1.689(4)
S2–C11	1.703(4)	S2–C8	1.725(4)
Cl1–C1	1.711(4)	Cl2–C4	1.707(4)
C1–S1–C4	90.6(2)	C8–S2–C11	90.8(2)
S1–C1–Cl1	114.9(2)	S1–C4–Cl2	119.7(3)
Br1–C11–S2	119.7(2)	Br1–C11–C10	126.7(3)
C2–C5–C6–C7	178.(4)	O1–C5–C6–C7	–0.8(7)
C5–C6–C7–C8	–179.8(4)	C8–S2–C11–Br1	–178.9(3)

The crystal packing does not present geometrical parameters corresponding to the classical hydrogen bonding [28], and is governed by non-conventional hydrogen bond-type intermolecular interactions. The structure of **5** is built up from the self-assembly of molecules via the C---H···O hydrogenbonding (Fig. 2 and Table 3). The C10---H10···O1 interactions

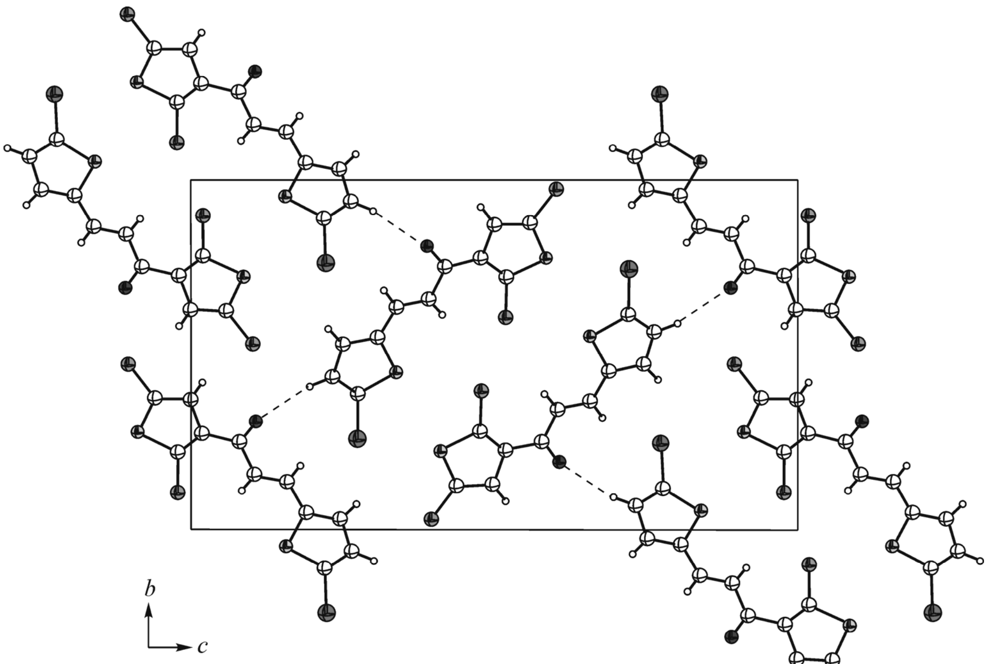


Fig. 2. Partial view of the crystal packing shows the hydrogen bonds formed (C---H···O).

TABLE 3. Hydrogen Bond Geometry (Å,deg.)

D---H···A	D---H	H···A	D···A	D---H···A
C10---H10···O1^{i}	0.9300	2.49	3.406(5)	167
C7---H7···O1	0.9300	2.43	2.769(6)	102
C6---H6····Cl1	0.9300	2.54	3.257(4)	134
C6---H6···S2	0.9300	2.84	3.193(4)	104

D – donor; A – acceptor; H – hydrogen.
Symmetry codes: ^{i} 1/2–*x*, –1/2+*y*, 1/2–*z*.

(1/2–*x*, –1/2+*y*, 1/2–*z*) form extended zigzag chains related by 2_1 screw axes running along the [010] direction. These chains may be described in a graph-set notation as C(8) [29, 30]. The network is reinforced by weak intermolecular non-conventional C7---H7···O1, C6---H6···Cl1, and C6---H6···S2 hydrogen bonds. These hydrogen bonds contribute to the stabilization of the crystal structurewhich packs with an efficiency of 71.4% of the filled space.

CONCLUSIONS

The new thiophene chalcone compound was synthesized by the Claisen-Schmidt condensation method. The structure was unambiguously assigned by X-ray diffraction studies. The IR, NMR, and HRMS results were consistent with the structural results. In the crystal structure of (*E*)-3-(5-bromothiophen-2-yl)-1-(2,5-dichlorothiophen-3-yl)-2-propen-1-one, the molecules are linked by C---H···O hydrogen bonds, forming extended zigzag chains running along the [010] direction. The crystal packing is completely dominated by cohesive weak interactions among the neighboring molecules producing an efficient packing with 71.4% of the occupied space.

J. Jamalis wishes to thank the Ministry of Higher Education (MOHE) for funding this research under the Research University Grant (RUP) with vote No. 07J48 and Fundamental Research Grant Scheme (FRGS) of vote numbers 4F448. This work was also supported by the Laboratorio de Rayos-X del Parque Tecnológico Guatiguará (PTG), Universidad Industrial de Santander (UIS), Colombia, and FONACIT (grant LAB-97000821), Venezuela.

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