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ORIGINAL PAPER

Isolation, Characterization and X-ray Structure Determination of 2,5-Bis(4-methylbenzylthio)-1,3,4-thiadiazole

Shahedeh Tayamon · Edward R. T. Tiekink · Farzad Nikpour · Thahira Begum S. A. Ravoof · Mohamad Ibrahim Mohamed Tahir · Karen A. Crouse

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Abstract The reaction of hydrazine hydrate with carbon disulfide and 4-methylbenzyl chloride in basic solution yielded 2,5-bis(4-methylbenzylthio)-1,3,4-thiadiazole ($C_{18}H_{18}N_2S_3$, compound **1**) in addition to the expected *S*-4-methylbenzyldithiocarbazate. The molecule has approximate twofold symmetry with the C=S bond lying on the pseudo axis. The five membered ring is planar with the three S atoms mutually syn, and with pendent 4-methylbenzylthio substituents; the dihedral angle between the terminal rings is 52.21(7)°. The compound **1** crystallizes in the triclinic space group $P\bar{1}$ with $a = 6.0139(3)$ Å, $b = 11.8694(7)$ Å, $c = 12.6330(7)$ Å, $\alpha = 72.583(5)°$, $\beta = 82.827(4)°$, $\gamma = 89.882(4)°$ and $Z = 2$.

Keywords Dithiocarbazate · 1,3,4-Thiadiazole · Supramolecular structure · Crystal structure

Introduction

During the past few decades, reports on substituted derivatives of the dithiocarbazate anion, $NH_2NHC(SR)S^-$, and their metal complexes have focused on differences in their structures [1, 2] and their biological activity towards fungi, bacteria and cancer cells [3–5]. In the presence of acid or base, 3-acyldithiocarbazic acid esters, *N*-aroyldithiocarbazates and their salts can convert to 1,3,4-oxadiazole/thiadiazole-2-thiones [6, 7]. Common synthetic methods such as cyclization of thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines, acylhydrazines, bithioureas have been used to synthesize thiadiazoles [7–9]. In general, to prepare 1,3,4-thiadiazole derivatives, appropriate rearrangements accompanied by ring closure and substitution are required [10]. 1,3,4-Thiadiazole ring systems are also of interest in medicine and agriculture as they have found application as dyes, in determination of trace elements and in the preparation of optically active liquid crystals and photographic materials [11, 12]. Many derivatives have been reported to be herbicides, insecticides, fungicides, bactericides, anthelmintics [13], antihypertensives, and anticonvulsives [14–16]. 1,3,4-Thiadiazole ring systems having different substituents at positions 2 and 5, have been isolated as by-products during crystallization of dithiocarbazate derivatives in our laboratory [17–19]. In continuation of these studies, herein we report the crystal structure and spectroscopic characterization of a new symmetric 2,5-disubstituted thiadiazole ring system, namely 2,5-bis(4-methylbenzylthio)-1,3,4-thiadiazole (**1**).

Experimental

Materials and Physical Measurements

All chemicals and solvents were of analytical grade and were used as received. The melting point was determined using an Electrothermal IA9100 digital melting point apparatus. Microanalyses for carbon, hydrogen, and nitrogen were

S. Tayamon · T. B. S. A. Ravoof · M. I. M. Tahir · K. A. Crouse (✉)
Department of Chemistry, Faculty of Science, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
e-mail: kacrouse@gmail.com; karen@upm.edu.my

E. R. T. Tiekink
Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia

F. Nikpour
Department of Chemistry, University of Kurdistan, Sanandaj, Iran

carried out using a LECO TruSpec CHN/CHNS instrument. The IR spectra were recorded using a Perkin-Elmer FT IR 1750X spectrophotometer (4,000–400 cm^{-1}). NMR spectra were acquired on a JOEL JNM-ECX500 MHz spectrometer in deuterated chloroform with TMS as the internal standard. All chemical shift values were recorded in ppm (δ). The mass spectrum was determined using a DIMS QP5050A Shimadzu Gas Chromatograph–Mass Spectrometer.

Isolation of 2,5-Bis(4-methylbenzylthio)-1,3, 4-thiadiazole

Crystals of the title compound suitable for X-ray analysis were isolated as a by-product from the preparation of S-4-methylbenzyldithiocarbazate (S-4MBDTC). The procedure was adapted from Ravoof et al. [20]. Potassium hydroxide (11.4 g, 0.2 mol) was dissolved in absolute ethanol (70 mL) to which hydrazine hydrate (10 g, 0.2 mol) was added followed by cooling in an ice salt bath to 0 °C. Carbon disulphide (15.2 g, 0.2 mol) was added drop wise with constant stirring over a period of 1 h. The two layers that subsequently formed were separated. The lower light brown layer was taken up in 40 % ethanol (60 mL) below 5 °C. The mixture was kept in an ice-bath and 4-methylbenzyl chloride (26.5 mL, 0.2 mol) was added drop wise with vigorous stirring. The major product (sticky, white S-4MBDTC) was filtered and left overnight to dry over anhydrous silica gel in a desiccator. S-4MBDTC, was filtered immediately after recrystallization from ethanol. The title compound, 2,5-bis(4-methylbenzylthio)-1,3,4-thiadiazole (**1**), precipitated from the filtrate after a period of days. Yield: 32 %, m.p. 132.2 °C. $C_{18}H_{18}N_2S_3$ calc. (found): C 60.30 (60.76), H 5.06 (5.13), N 7.81 (8.05). ^{1}H NMR [500 MHz, $CDCl_3$, δ (ppm)]: 7.26 (d, 4H, J = 8 Hz, C*H*–C–CH_3), 7.11 (d, 4H, J = 8 Hz, C*H*–C–CH_2), 4.44 (s, 4H, CH_2), 2.31 (s, 6H, CH_3). ^{13}C NMR [500 MHz, $CDCl_3$, δ (ppm)]: 164.79 (2C, thiadiazole-C), 137.72 (*C*–CH_3 in benzene rings), 132.58 (*C*–CH_2), 129.40, 129.05 (C of benzene rings), 38.20 (CH_2S), 21.13 (CH_3–Bz).

X-ray Crystallography

A single crystal of **1** was selected and mounted in a loop using perfluoropolyether oil and cooled rapidly to 100 K in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat [21] with a nominal stability of 0.1 K. Diffraction data were measured using an Agilent Gemini diffractometer (graphite monochromated CuK_α radiation, λ = 1.54180 Å) so that $2\theta_{max}$ was 142.7° [22]. The structure was solved by direct methods with SHELXS-97 [23] and refined by a full-matrix least-squares procedure on F^2 using SHELXL-97 [23] with anisotropic displacement parameters for non-hydrogen atoms, hydrogen atoms in their calculated positions and a weighting scheme of the form $w = 1/[\sigma^2(F_o^2) + 0.1P^2]$ where $P = (F_o^2 + 2F_c^2)/3$. Crystal data and refinement details are given in Table 1. Figure 2, showing the atom labeling scheme, was drawn with 50 % displacement ellipsoids using ORTEP-3 for Windows [24] and the remaining figures were drawn with DIAMOND [25] but with arbitrary spheres. Additional data manipulation and interpretation were accomplished using WinGX [24] and PLATON [26].

Table 1 Crystal data and refinement details for (**1**)

Formula	$C_{18}H_{18}N_2S_3$
Formula weight	358.52
Crystal habit, color	Prism, colorless
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	6.0139 (3)
b (Å)	11.8694 (7)
c (Å)	12.6330 (7)
α (°)	72.583 (5)
β (°)	82.827 (4)
γ (°)	89.882 (4)
Volume ($Å^3$)	853.09 (8)
Z	2
Density (calculated, g cm^{-3})	1.396
Absorption coefficient (mm^{-1})	3.959
F(000)	376
Crystal size (mm)	0.18 × 0.21 × 0.36
θ range for data collection (°)	3.7–71.4
Reflections collected	11,074
Independent reflections	3,266
R_{int}	0.023
Reflections with $I \geq 2\sigma(I)$	3,086
Number of parameters	210
Goodness-of-fit on F^2	0.99
Final *R* indices [$I \geq 2\sigma(I)$]	$R_1 = 0.033$, $wR_2 = 0.112$
R indices [all data]	$R_1 = 0.035$, $wR_2 = 0.114$
Largest difference peak and hole ($Å^{-3}$)	0.36, −0.33
CCDC deposition no.	926,368

Results and Discussion

Dithiocarbazate salts are generally produced on treatment of substituted hydrazines with carbon disulfide at low temperature in the presence of base. Acidification of dithiocarbazate solutions can afford free dithiocarbazic acids (NH_2–NH_2–CS_2H) that precipitate, for example, when the potassium salt is treated with dilute HCl at 0 °C. It is also known that the so called dithiocarbazate route is one of the synthetic pathways to 1,3,4-thiadiazole derivatives [10].

Cyclized thiadiazole compounds have also been isolated as co-products during synthesis of dithiocarbazate derivatives [17] and have been produced during recrystallization of S-substituted dithiocarbazates in our laboratory [18, 19]. The title compound, **1**, was formed during the preparation of (S-4MBDTC) where the cyclization reaction appears to have occurred during the addition of carbon disulphide. It is almost impossible to obtain pure zwitterionic NH_3^+–NH_2–CS_2^- as it evolves hydrogen sulfide to give 1,3,4-thiazolidine-2,5-dithione [27]. Since hydrazine possesses two primary amino groups, reaction with carbon disulfide could take place at both sites. The general proposed mechanism for the formation of the cyclized product is given in Fig. 1.

Spectral evidence and elemental analyses confirmed the presence of a thiadiazole-like product as, for example, ν(C=O), ν(C=S), and ν(N–H) bands were not observed in the spectrum of **1**. The appearance of weak bands at 1611, 2920, and 3029 cm^{-1} indicate the presence of C=N, aliphatic CH and aromatic CH, respectively. In the NMR spectra, the chemical shifts (^1H and ^{13}C), multiplicity and integration (^1H) observed in $CDCl_3$ solution is in line with the solid state structure (see below). In particular, there is no evidence in the ^1H NMR spectrum for the presence of N–H or S–H type protons. The molecular ion peak is apparent at m/z 358. The methylbenzyl fragment (m/z 105) appeared as the base peak. Another prominent peak was at m/z 162 and is ascribed to the disulfurthiadiazole ion, $[C_2N_2S_3]^{+\cdot}$. The structure was unambiguously confirmed by X-ray crystal structure determination.

The molecular structure of **1** is shown in Fig. 2 and selected geometric parameters are collected in Table 2. The central 1,3,4-thiadiazole ring is strictly planar with the r.m.s deviation of the fitted atoms being 0.002 Å. Within

Table 2 Selected geometric parameters (Å, °) for (**1**)

Atoms	Parameter	Atoms	Parameter
S1–C1	1.7461(15)	S1–C3	1.8302(15)
S2–C1	1.7395(15)	S2–C2	1.7438(14)
S3–C2	1.7440(15)	S3–C11	1.8260(15)
N1–N2	1.3913(17)	N1–C1	1.298(2)
N2–C2	1.296(2)		
C1–S1–C3	99.79(7)	C1–S2–C2	86.10(7)
C2–S3–C11	100.64(7)	C1–N1–N2	112.25(12)
C2–N2–N1	112.46(12)	S1–C1–S2	120.06(9)
S2–C2–S3	120.37(9)	S1–C1–N1	114.69(11)
S2–C2–N2	114.50(11)	S1–C3–C4	108.04(10)
S3–C11–C12	106.61(10)		

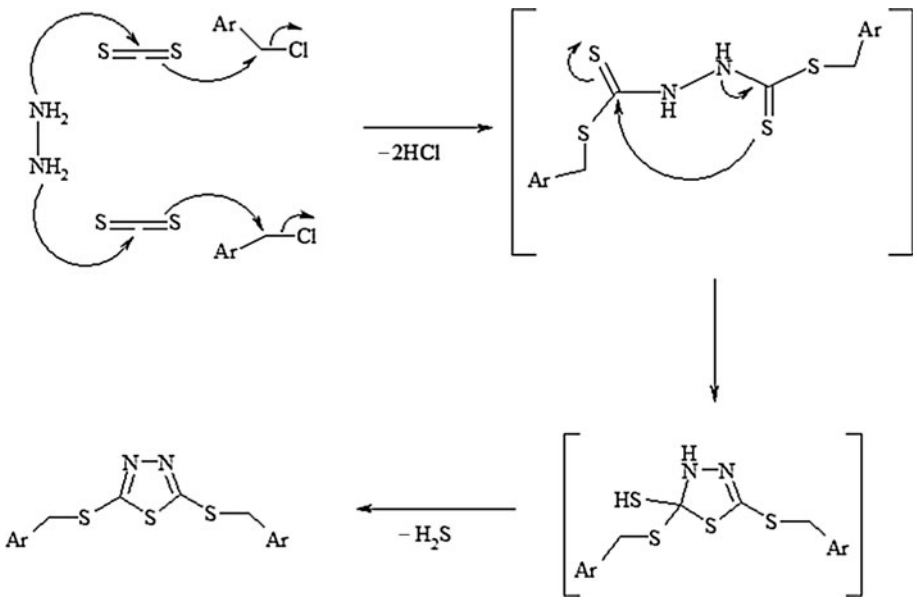

Fig. 1 Proposed reaction mechanism for the formation of cyclized thiadiazole derivatives from dithiocarbazates

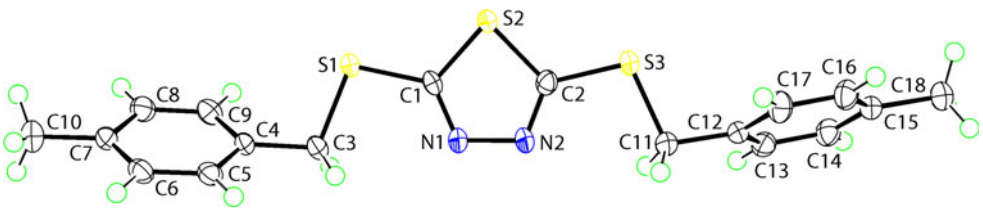

Fig. 2 Molecular structure of the (**1**) showing atom labeling scheme. Displacement ellipsoids are drawn at the 70 % probability level (color figure online)

Table 3 Intermolecular interactions (A–H···B; Å, °) operating in the crystal structure of (**1**)

A	H	B	H···B	A–H···B	A···B	Symmetry operation
C3	H3A	Cg(C4–C9)	2.71	132	3.4507(16)	2−x, 2−y, −z
C9	H9	Cg(S2,N1,N2,C1,C2)	2.94	163	3.8557(17)	1 + x, y, z
C10	H10B	Cg(C12–C17)	2.94	167	3.8985(18)	2 + x, 1 + y, z
C17	H17	Cg(S2,N1,N2,C1,C2)	2.80	160	3.7063(17)	−1 + x, y, z

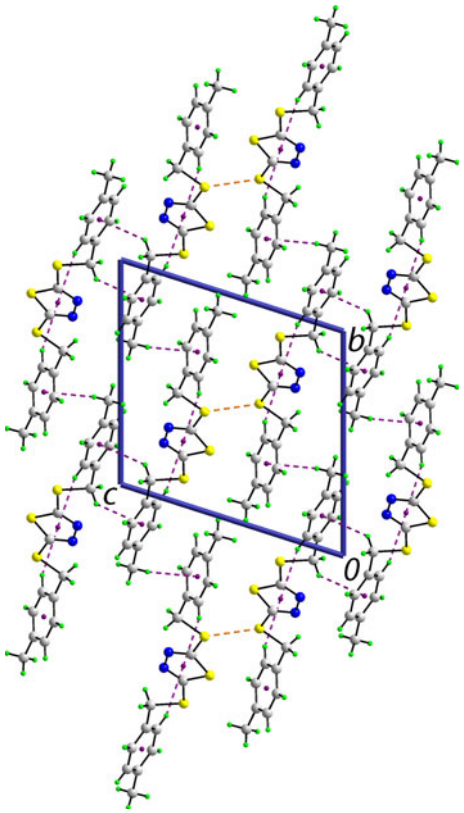

Fig. 3 View in projection down the a-axis of the unit cell contents of (**1**). The C–H···π and S···S contacts are shown as purple and orange dashed lines, respectively (color figure online)

the ring the N–N and C=N bond lengths are consistent with the cyclic product shown in Fig. 1, and the sequence of intra-ring angles is C–S–C<S–N–N<C–C–N, Table 2, with the difference between the latter two angles subtended at nitrogen and carbon being about 2° only. The C–S bond lengths involving the ring carbons are significantly shorter than the exocycliuc S–C bond lengths, Table 2. Two pendent S-bound 4-methylbenzylthio residues are connected to the ring at the C1 and C3 atoms. The phenyl groups in these are inclined differently with respect to the five membered ring forming dihedral angles of 70.28(7) and 64.87(7)°, respectively; the dihedral angle between the phenyl rings is 52.21(7)°. Overall, differences in chemically equivalent geometric parameters are not significant and the molecule has approximate twofold symmetry with the S2 atom lying on the axis. In terms of global conformation, the three sulfur atoms in **1** are mutually syn, lying to the same side of the molecule.

In the crystal packing, molecules of **1** assemble into supramolecular layers parallel to (012) via edge-to-face C–H···π interactions (Table 3). Each of the aromatic rings function as acceptor with the 1,3,4-thiadiazole ring forming two such interactions, and the donors are either phenyl-, methylene- or methyl-H, Table 3. Connections between the layers are of the type S···S with the S3···S3^{i} separation of 3.4587(5) Å being less than the sum of the van der Waals radii, i.e., 3.60 Å [28]; symmetry operation i: −x, 1−y, 1−z, Fig. 3.

While not numerous there are precedents for the structure of **1** in the crystallographic literature [29], notably 2,5-bis(benzylthio)-1-thia-3,4-diazacyclopenta-2,4-diene [30] and 4,4′-[(1,3,4-thiadiazole-2,5-diyl)bis(thiomethylene)]dibenzonitrile [31]. In the same way, the coordination chemistry of such molecules is still in its infancy. The observation of both monodentate *N*- and bidentate *N*,*N*-bridging modes have been observed in some rhenium complexes [32].

Conclusion

A new molecule containing a 1,3,4-thiadiazole ring system, arising from the in situ cyclization of its authenticated dithiocarbazate precursor, has been fully characterized. In the molecular structure the central core is strictly planar but the terminal aryl groups are twisted out of this plane. The sulfur atoms are mutually syn.

Supplementary Material

CCDC-926368 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax +44(0)1223-336033; email: deposit@ccdc.ccam.ac.uk].

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