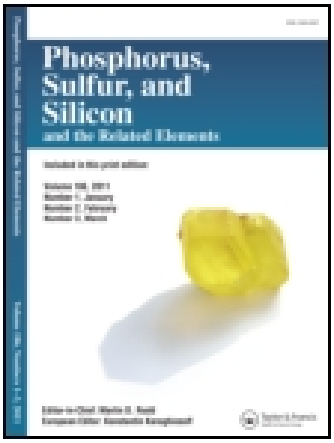

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Synthesis, Crystal Structure, and Fungicidal Activity of a Novel 1,2,3-Thiadiazole Compound

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SYNTHESIS, CRYSTAL STRUCTURE, AND FUNGICIDAL ACTIVITY OF A NOVEL 1,2,3-THIADIAZOLE COMPOUND

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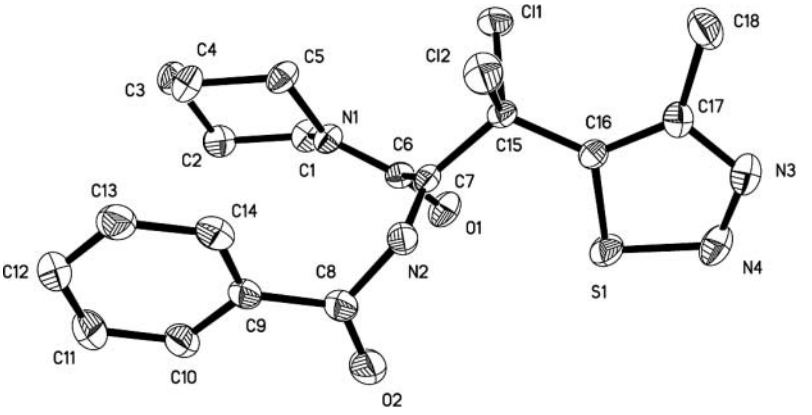
GRAPHICAL ABSTRACT



Abstract *A new 1,2,3-thiadiazole compound, $C_{18}H_{18}Cl_2N_4O_2S$, has been synthesized and the crystal structure was determined by single crystal X-ray diffraction study. The fungicidal activity of the title compound was determined and the results showed that it displays moderate fungicidal activity.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Crystal structure; synthesis; 1,2,3-thiadiazole; fungicidal activity

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INTRODUCTION

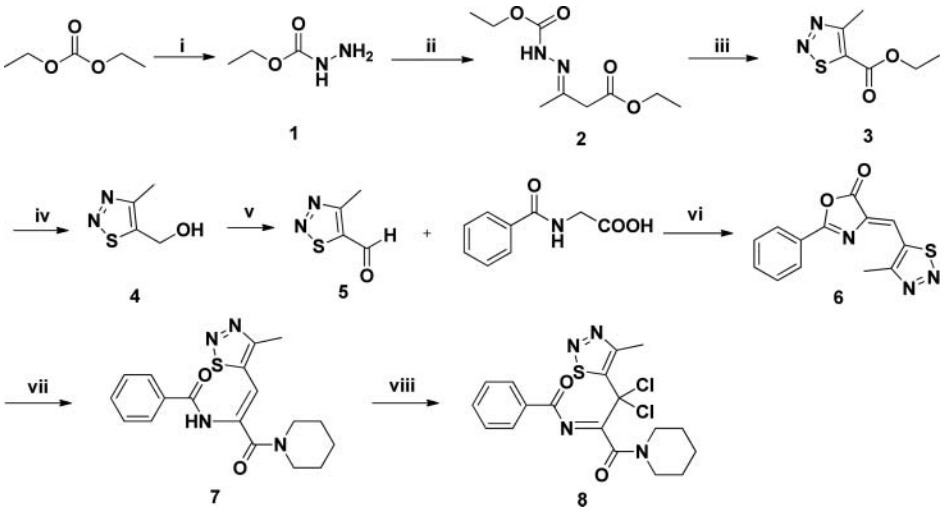
In recent years, sulfur and nitro linked heterocycles has received considerable attention in medicinal and pesticidal fields,[1–5] because of their various activities, such as KARI,[6] herbicidal,[7] fungicidal,[8] antiviral,[9] and antitubercular activities.[10] It is reported that 1,2,3-thiadiazole has beneficial medicinal and agricultural applications. Due to its good bioactivity and usefulness as intermediates in organic synthesis, the chemistry of the 1,2,3-thiadiazole ring has been widely studied. For example, many 1,2,3-thiadiazoles exhibited plant inducer activity,[11] anti-HBV activity,[12] fungicidal activity,[13] and insecticidal activity.[14] 1,2,3-Thiadiazoles as examples of pesticide precursors have become one of the area of focus of developing agrochemicals in academia and industry. The piperidine ring also exhibited excellent biological properties, such as antifungal,[15] antimalarial[16] and antileukemic activities,[17] GABA inhibitors,[18] VLA-4 inhibitors,[19] and herbicidal activity.[20] A large variety of piperidine derivatives were successfully applied to commercial medicine or pesticide, such as mepiquat chloride,[21] acetamiprid,[22] droperidol,[23] haloperidol,[24] and fentanyl citrate.[25]

In view of these facts, and also as a part of our work on the development of bioactive heterocyclic compounds, herein a 1,2,3-thiadiazole compound was synthesized and its single crystal structure was determined.

RESULTS AND DISCUSSION

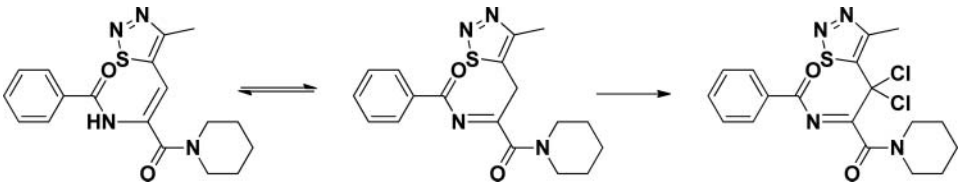
Chemistry

The synthesis procedure for title compound **8** is shown in Scheme 1. The intermediates **1**, **2**, **3**, **4**, **5** were synthesized according to our reported reference.[12] According to our method, the title compound **8** cannot be obtained. On the other hand, if the reaction temperature was under 0 °C, the mono chloro compound was obtained. In the process of optimizing the reaction, the reaction temperature was changed to room temperature or reflux. The title compound **8** was obtained at room temperature. The proposed reaction procedure is shown



Scheme 1 The synthetic route of title compound.

in Scheme 2. The compound was also identified by ^{1}H NMR. The measured elemental analyses were also consistent with the corresponding calculated ones.



Scheme 2 The proposed reaction route.

Crystal Structure

The selected bond lengths and bond angles in Table 2. The selected dihedral angles are shown in Table S1. The molecular structure of the title compound is shown in Figure 1. The molecular packing of the molecule is shown in Figure **S1**. The π-π stacking is shown in Figure **S2**.

Generally, the average bond lengths and bond angles of ring systems (phenyl and 1,2,3-thiadiazole) are normal ranges. The C6—N1 bond [1.33 Å] is shorter than a normal C—N single bond (1.47 Å), which shows that C6—N1 is conjugated with the O6—C1 double bond. However, the C7=N2 bond [1.25 Å] is similar with the general C=N double bond length of 1.27 Å.

Table 1 Crystal structure and data refinement parameters

Compound	**8**
Empirical formula	$C_{18}H_{18}Cl_2N_4O_2S$
Formula weight	425.32
Crystal system/Space group	Triclinic, *P*-1
a/Å	8.285 (3) Å
b/Å	10.072 (3) Å
c/Å	11.828 (4) Å
α/°	99.094 (5)°
β/°	105.839 (5)°
γ/°	92.507 (5)°
V/Å^3	933.7 (5) Å^3
Z	2
D_{calc} (g/cm^3)	1.513 Mg m^{-3}
μ (mm^{-1})	0.4800
Crystal size (mm)	0.32 × 0.30 × 0.26
Color/Shape	Colorless, prism
Temp (K)	293(2)
Theta range for collection	3.4–26.4°
Reflections collected	5446
Independent reflections	3794 [R(int) = 0.0148]
Data/restraints/parameters	3794/0/244
Goodness of fit on F^2	1.070
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0324$, w$R2 = 0.0831$
R indices (all data)	$R1 = 0.0478$, w$R2 = 0.0912$
Largest difference peak/hole	0.250 and −0.211 e A^{-3}

Table 2 Selected bond lengths (Å) and angles (°) for the title compound

Bond lengths	Å	Bond angles	(°)
Cl(1)−C(15)	1.7875(1)	N(4)−S(1)−C(16)	93.07(10)
Cl(2)−C(15)	1.7672(1	C(6)−N(1)−C(1)	118.77(16)
S(1)−N(4)	1.650(2)	C(6)−N(1)−C(5)	123.06(15)
S(1)−C(16)	1.6774(1)	N(1)−C(5)−C(4)	111.35(16)
O(1)−C(6)	1.218(2)	C(10)−C(9)−C(8)	118.18(19)
O(2)−C(8)	1.195(3)	N(4)−N(3)−C(17)	113.98(18)
N(1)−C(6)	1.327(2)	N(1)−C(1)−C(2)	110.88(16)
N(1)−C(1)	1.461(2)	N(3)−C(17)−C(18)	118.11(19)
N(1)−C(5)	1.462(2)	C(16)−C(17)−C(18)	128.76(19)
N(2)−C(7)	1.251(2)	N(3)−N(4)−S(1)	111.71(14)
N(2)−C(8)	1.413(3)	O(1)−C(6)−N(1)	125.52(18)
N(3)−N(4)	1.287(3)	O(1)−C(6)−C(7)	116.41(17)
N(3)−C(17)	1.357(3)	N(1)−C(6)−C(7)	117.99(16)
C(1)−C(2)	1.505(3)	N(2)−C(7)−C(6)	124.18(17)
C(15)−C(16)	1.490(2)	O(2)−C(8)−N(2)	119.98(19)
C(16)−C(17)	1.360(3)	O(2)−C(8)−C(9)	124.53(19)
C(17)−C(18)	1.481(3)	N(2)−C(8)−C(9)	115.40(18)

As shown in Figure 1, the 1,2,3-thiadiazole rings (N3, N4, S1, C16, C17) and phenyl rings (C9, C10, C11, C12, C13, C16) are fairly planars with plane equation $1.421x + -5.365y + 9.836z = 7.4185$ ($-1.347x + -4.201y + 11.354z = 9.4842$), and the largest deviation from the least squares plane is 0.0029 nm (0.0056 nm). Meanwhile, the 1,2,3-thiadiazole ring is parallel with the phenyl ring (C1∼C6) with the angles of 20.4°. From the molecular structure, it can be seen that both groups on the N atoms of piperidine ring are in the e-bond positions of chair conformation in the six-member ring. The X-ray analysis also reveals that, in this compound, the benzene ring and 1,2,3-thiadiazole ring are on the opposite sides of the C=N double bond (Figure 1). The torsion angle of

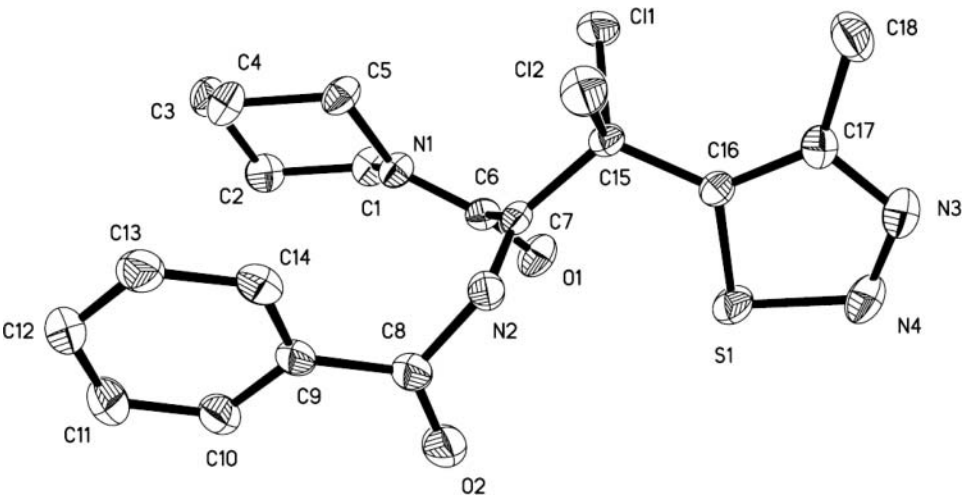


Figure 1 Molecular structure of the title compound, showing displacement ellipsoids drawn at the 30% probability level.

C(15)−C(7)−N(2)−C(8) is 173.68°, which indicates that the C=N double bond is in the (*E*)-configuration.

The intermolecular edge-to-face π-π stacking appears between the piperidine ring and the phenyl ring C9∼C14 in another adjacent molecule (Figure S4), in which the distance of H4B and the centroid of phenyl ring C9∼C14 is 2.839 Å. These interactions can help to further stabilize the crystal structure.

Fungicidal Activity

The primary bioassay shows the title compound exhibits a moderate inhibiting activity toward Alternaria solani, Gibberella sanbinetti, Phytophthora infestans (Mont.) de Bary, Botrytis cinerea, Rhizoctonia solanii, Phytophthora capsici Leonian, Fusarium oxysporum, Physalospora piricola Nose, and Cercospora arachidiaola Hori. Its inhibition rates to Alternaria solani, Gibberella sanbinetti, Phytophthora infestans (Mont.) de Bary, Botrytis cinerea, Rhizoctonia solanii, Phytophthora capsici Leonian, Fusarium oxysporum, Physalospora piricola Nose, and Cercospora arachidiaola Hori reach 17.4%, 32.3%, 32.3%, 43.5%, 30.3%, 36.1%, 26.9%, 25.8%, and 15.8% at 50 μg/mL respectively.

EXPERIMENTAL

Materials and Methods

All the reagents were of analytical grade. Melting points were determined using an X-4 apparatus and uncorrected. ^{1}H NMR spectra were measured on a Bruker AC-P500 (300 Hz) instrument using tetramethylsilane (TMS) as an internal standard and $CDCl_3$ as solvent. Elemental analyses were performed on a Vario EL elemental analyzer. Crystallographic data of the compound were collected on a Bruker SMART 1000 CCD diffractometer.

4-methyl-1,2,3-thiadiazole-5-carbaldehyde (5). Compound **5** was prepared as a white solid using commercially available acetyl ethyl acetate as the starting material according to the literature.[12]

(E)-4-((4-methyl-1,2,3-thiadiazol-5-yl)methylene)-2-phenyloxazol-5(4H)-one (6). To a 50-mL three-necked round-bottomed flask equipped with a reflux condenser bearing a calcium chloride tube were placed benzoylglycine (3.36 g, 17.9 mmol), **5** (2.32 g, 17.9 mmol), anhydrous sodium acetate (1.54 g, 17.9 mmol), and acetic anhydride (5.47 g, 53.6 mmol). The mixture was heated at 138 °C for 10 min, then lowered to 95 °C–100 °C for an additional 2 h. After being cooled to 80 °C, the reaction mixture was treated with ethanol (3 mL) and cooled to room temperature. The product precipitated out of solution, and after standing overnight, the solid was collected, washed with ethanol (2 × 10 mL) and hot water (3 × 5 mL), and dried to obtain **6** (2.81g, 57% yield) as a red solid, m.p. 233 °C–235 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.90 (s, 3H, 4-methyl-thiadiazole), 7.40 (s, 1H, −CH=), 7.57–8.30 (m, 5H, Ph).

(E)-N-(1-(4-methyl-1,2,3-thiadiazol-5-yl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide (7). To a solution of **6** (1.4 g, 5.1 mmol) in $CHCl_3$ (20 mL) was stirred under an ice bath. A solution of piperidine (5.6 mmol) in $CHCl_3$ (10 mL) were added dropwise, the mixture was allowed to stir at room temperature for 1.5 h. After standing overnight, the resulting solution was filtered, the filtered solution was evaporated under reduced pressure to afford **7**, as a yellow solid, yield 69%, m.p. 175 °C–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92-1.75 (m, 6H, $-CH_2-CH_2-CH_2-$), 2.59 (s, 3H,

4-methyl-thiadiazole), 3.29–3.72 (m, 4H, $-CH_2-N-CH_2-$), 7.24–7.81 (m, 5H, Ph+1H, $-CH=$), 9.15(s, 1H, $-NH-$). Anal. calcd for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72; found: C,60.76; H, 5.45; N, 15.76.

(E)-N-(1,1-dichloro-1-(4-methyl-1,2,3-thiadiazol-5-yl)-3-oxo-3-(piperidin-1-yl)propan-2-ylidene)benzamide (8). To a solution of **7** (0.5 g, 1.39 mmol) in $CHCl_3$ (10 mL) was added chlorine (0.32 g, 2.0 mmol) in CCl_4 (20 mL) at room temperature. The mixture was stirred at room temperature for 2 h and then $CaCO_3$ (0.07 g, 0.7 mmol) was added, the resulting solution was stirred for 5 h at room temperature. The residue was subjected to silica gel column chromatography to afford compound **8**, white solid, yield 71%, m.p. 122 °C–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.79–1.68 (m, 6H, $-CH_2-CH_2-CH_2-$), 2.96 (s, 3H, 4-methyl-thiadiazole), 3.65–3.87 (m, 4H, $-CH_2-N-CH_2-$), 7.22–7.85 (m, 5H, Ph). Anal. calcd for $C_{18}H_{18}Cl_2N_4O_2S$: C, 50.83; H, 4.27; N, 13.17; found: C,50.79; H, 4.39; N, 13.10.

Crystal Structure Determination

The prism-shaped single crystal of the title compound was obtained by recrystallization from EtOH. The crystal with dimensions of 0.32 mm × 0.30 mm × 0.26 mm was mounted on a Bruker SMART 1000 CCD area-detector diffractometer with a graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) by using a Phi scan modes at 293(2) K in the range of $1.82^\circ \leq \theta \leq 26.43^\circ$. A total of 5546 reflections were collected, of which 3794 were independent ($R_{int} = 0.118$) and 2973 were observed with $I > 2\sigma(I)$. The calculations were performed with SHELXS-97 program[26] and the empirical absorption corrections were applied to all intensity data. The nonhydrogen atoms were refined anisotropically. The hydrogen atoms were determined with theoretical calculations and refined isotropically. The final full-matrix least squares refinement gave $R1 = 0.0324$ and w$R2 = 0.0831$ ($w = 1/[\sigma^2(F_o^2) + (0.039P)^2 + 0.2892P]$ where $P = (F_o^2 + 2F_c^2)/3$, $S = 1.07$, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.25$ and $\Delta\rho_{min} = -0.21$ e Å^{-3}. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-Ray Crystallography.[27] A summary of the key crystallgraphic information were given in Table 1.

Bioassay of Fungicidal Activities

The method for testing the primary biological activities was performed in an isolated culture and the details are reported in the supplemental materials.

Supplementary material, CCDC-832172, 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, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

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