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Synthesis, Crystal Structure and Bioactivity of *N*-(5-propyl-1,3,4-thiadiazol-2-yl)cyclopropanecarboxamide

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A new 1,3,4-thiadiazole compound with m.f. $C_9H_{13}N_3OS$, has been synthesized and confirmed by ^1H NMR and HRMS. The single crystal structure of the 1,3,4-thiadiazole compound was determined by a single crystal X-ray diffraction study. The crystal belongs to the triclinic system, space group P-1 with a = 10.238(2), b = 10.325(2), c = 10.560(2) Å, α = 104.09(3), β = 109.50(3), γ = 93.40(3)º, Z = 4, V = 1008.4(3)Å^3, Mr = 211.28, Dc = 1.392 g/cm^3, S = 0.98, μ = 0.29 mm^{-1}, F(000) = 448, the final R1 = 0.0970 and wR^2 = 0.2147 for 1776 were observed with I > 2σ(I). X-ray indicated that two intermolecular hydrogen bonds N1-H1···N5, N4-H4···N2 were observed. The preliminary biological test shown that the synthesized compound has moderate herbicidal activity against *Brassica campestris*.

Key Words: Crystal structure, Synthesis, 1,3,4-thiadiazole, Herbicidal activity.

INTRODUCTION

Recent years, sulfur and nitro linked heterocycles has received considerable attentions in medicinal and pesticidal field[1-6], due to their various applications. 1,3,4-Thiadiazoles had broad-spectrum biological activity which are widely applied in medicinal and agricultural applications. So synthesis of broader spectrum and highly bioactive 1,3,4-thiadiazole compounds becomes the hot spot in the agricultural and medicinal chemistry field. For example, many 1,3,4-thiadiazoles exhibit antibacterial activity[7], anti-alzheimer activity[8], fungicidal activity[9], anticancer activity[10]. Antimycobacterial activity[11], nitrification Inhibitor[12]. Also 2-amino-5-substituted-1,3,4-thiadiazoles are very useful starting materials for the synthesis of various bioactive molecules[13-15]. Many medicine or pesticide containing amide group and 1,3,4-thiadiazole moiety. On the other hand, cyclopropane is a active group in the drug design[16-18]. In view of these facts and also as a part of our work on the development of bioactive heterocyclic compounds, herein *N*-(5-propyl-1,3,4-thiadiazol-2-yl)cyclopropanecarboxamide was synthesized and its single crystal was also determined. The biological activity was determined.

EXPERIMENTAL

All the reagents are analytical grade. Melting points were determined using an X-4 apparatus and were uncorrected. ^1H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using TMS as an internal standard and $CDCl_3$ as solvent. HRMS data was obtained on a FTICR-MS instrument (Ionspec 7.0T). Crystallographic data of the compound were collected on a rigaku saturn diffractometer.

Synthesis: The acid chloride was prepared according the reference[13]. Dropwise the acid chloride was added to 2-amino-5-propyl-1,3,4-thiadiazole (7.50 mmol), then vigorously stirred at ambient temperature for 4 h. The corresponding amide 7 precipitated immediately. The product was filtered, washed with THF, dried and recrystallized from EtOH-H_2O to give the title compounds **7**. White crystal, yield 84.5 %, m.p. 175-176 ºC; ^1H NMR ($CDCl_3$) δ: 1.02 (t, 3H, CH_3), 1.05-1.21 (m, 4H, cycloprane-CH_2), 1.81 (m, 2H, CH_2), 2.25-2.31 (m, 1H, cycloprane-CH), 2.98 (t, 2H, CH_2), 13.43 (s, 1H, NH); FTICR-MS for $C_9H_{13}N_3OS$: found 210.0704, calcd. 210.0707.

Structure determination: The prism-shaped single crystal of the title compound was obtained by recrystallization from EtOH. The crystal with dimensions of 0.20 mm × 0.16 mm × 0.12 mm was mounted on a Bruker SMART 1000 CCD area-detector diffractometer with a graphite-monochromated MoKα radiation (λ = 0.71073Å) by using a Phi scan modes at 113(2) K in the range of 2.06º ≤ θ ≤ 25.02º. A total of 7491 reflections were collected, of which 3544 were independent (R_{int} = 0.1576) and 1776 were observed with I > 2σ(I). The calculations were performed with SHELXS-97 program[19] and the empirical absorption corrections were applied to all intensity data. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were determined with theoretical calculations and refined isotropically. The final full-matrix least

squares refinement gave R1 = 0.0970 and wR2 = 0.2147 ($w = 1/[\sigma^2(F_o^2) + (0.0901P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$), S = 0.98, $(\Delta/\sigma)_{max} = 0.004$, $\Delta\rho_{max} = 0.84$ and $\Delta\rho_{min} = -0.68$ e Å^{-3}. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-ray crystallography[20]. A summary of the key crystallgraphic information were given in Table-1.

TABLE-1
CRYSTAL DATA OF THE TITLE COMPOUND

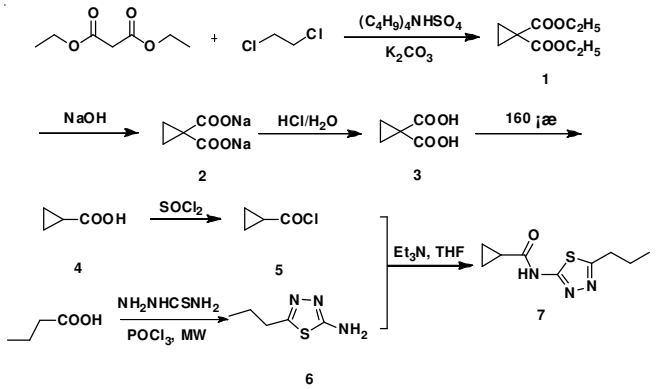
Empirical Formula	$C_9H_{13}N_3OS$
Formula weight	211.28
T/K	113(2)
λ/nm	0.071073
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 10.238(2) Å α = 104.09(3)º b = 10.325(2) Å β = 109.50(3)º c = 10.560(2) Å γ = 93.40(3)º
V/nm^3	1008.4(3) Å^3
Z	4
Calculated density/(g*cm^{-3})	1.392 Mg m^{-3}
Absorption coefficient (mm^{-1})	0.292
F(000)	448
Theta range for data collection	2.06 to 25.02 deg
Reflections collected / unique	7491 / 3544 [R_{int} = 0.1576]
Final R indices [I>2σ(I)]	R1 = 0.0970, wR2 = 0.2147
R indices (all data)	R1 = 0.1511, wR2 = 0.2522

Biological activity: The herbicidal activities were determined according to the references.

RESULTS AND DISCUSSION

The cyclopropane-1,1-dicarboxylic acid, prepared from 1,2-dichlorethane and diethyl malonate was cyclized for 16 h at refluxing temperature. Microwave assistant irradiation was applied which shortened the reaction time to 40 min. If the 1,2-dichlorethane changed to 1,2-dibromoethane, the reaction time is short. The cyclopropane-1,1-dicarboxylic acid was obtained from the hydrolysis of diethyl cyclopropane-1,1-dicarboxylate, but the yield of this step is low, about 50 %. Cyclopropanecarbonyl chloride was prepared from the cyclopropane dicarboxylic acid and $SOCl_2$, without isolation further reacted with 2-amino-5-propyl-1,3,4-thiadiazole at room temperature[13] (**Scheme-I**).

Herbicidal activities: The herbicidal activity results of the title compounds against *Echinochloa crusgalli* and *Brassica campestris* were determined. Its inhibition rates to



Scheme-I: Synthetic route of title compound

Echinochloa crusgalli and *Brassica campestris* reach 6.2 %, 38.4 % at 50 μg/mL and 0 %, 34.8 % at 10 g/mL respectively. The title compounds exhibit moderate herbicidal activities against *Brassica campestris* at 100 ppm. On the other hand, the title compounds exhibit no herbicidal activity against *Echinochloa crusgalli*.

Crystal structure: The selected bond lengths and bond angles are given in Table-2. The molecular structure of the title compound is shown in Fig. 1. The molecular packing of the molecule is shown in Fig. 2.

TABLE-2
SELECTED BOND LENGTHS (Å) AND BOND ANGLES (°)

Bond	Dist.	Angle	(°)
S(1)-C(5)	1.723(5)	C(5)-S(1)-C(6)	86.4(2)
S(2)-C(14)	1.728(5)	C(4)-N(1)-C(5)	123.7(4)
N(1)-C(4)	1.356(6)	C(5)-N(2)-N(3)	112.7(4)
N(2)-N(3)	1.401(5)	C(14)-N(5)-N(6)	112.9(4)
N(4)-C(14)	1.379(6)	C(2)-C(1)-C(3)	60.3(3)
N(5)-N(6)	1.388(5)	O(1)-C(4)-N(1)	121.3(4)

Symmetry transformation: a: *x*, *y*+1, *z*; b: –*x*, *y*, –*z*+1/2; c: –*x*, –*y*+1, –*z*

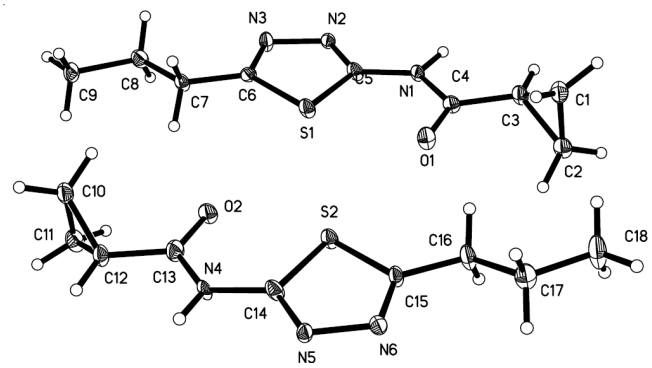


Fig. 1. Molecular structure of the title compound, showing displacement ellipsoids drawn at the 30% probability level

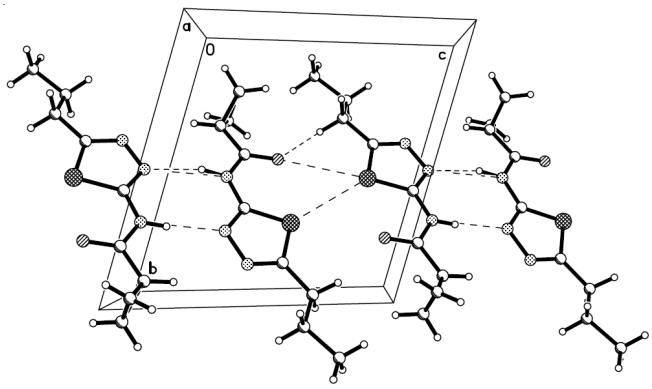


Fig. 2. Pack of title compound

Generally, the average bond lengths and bond angles of ring system (1,2,4-thiadiazole) are normal ranges. However, the C5 = N2 bond [1.295(6) Å] and C6 = N3 bond [1.307(6) Å] are similar with the general C=N double bond length of 1.27 Å[21-23]. The amide bond are normal, which is similar with the reported references[24-27]. As shown in Fig. 1, the 1,2,3-thiadiazole ring (N2, N3, S1, C5, C6) is fairly planar with mean deviation of 0.0035 Å. As shown in Fig. 2, intermolecular N-H···N hydrogen bonds stabilize the solid-state structure. The

title compound has an extensive network of hydrogen bonding involving the two acceptor atoms N. In the bc plane, they are linked together by N1-H1···N5, N4-H4···N2 hydrogen bonds. This hydrogen-bonding sequence is repeated to form a ring. The ring is shaped like a decagon and has two N1 atoms at the vertices, leading to a hydrogen-bond network defining cyclic motifs denoted R^2_2 (6) (Table-3).

TABLE-3
HYDROGEN BOND LENGTHS (Å) AND BOND ANGLES (°)

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠DHA
N(1)-H(1)...N(5)#1	0.904(10)	2.03(2)	2.896(6)	160(5)
N(4)-H(4)...N(2)#2	0.894(10)	2.019(13)	2.909(5)	174(4)

Symmetry transformations used to generate equivalent atoms: #1 x, y, z+1 #2 x,y, z-1

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