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

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(Received: 28 September 2012;

Accepted: 18 July 2013)

AJC-13817

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, $\alpha = 104.09(3)$, $\beta = 109.50(3)$, $\gamma = 93.40(3)^\circ$, $Z = 4$, $V = 1008.4(3)$ Å³, $Mr = 211.28$, $D_c = 1.392$ g/cm³, $S = 0.98$, $\mu = 0.29$ mm⁻¹, $F(000) = 448$, the final $R1 = 0.0970$ and $wR^2 = 0.2147$ for 1776 were observed with $I > 2\sigma(I)$. X-ray indicated that two intermolecular hydrogen bonds $N1-H1 \cdots N5$, $N4-H4 \cdots N2$ 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 field¹⁻⁶, 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 activity⁷, anti-alzheimer activity⁸, fungicidal activity⁹, anticancer activity¹⁰. Antimycobacterial activity¹¹, nitrification Inhibitor¹². Also 2-amino-5-substituted-1,3,4-thiadiazoles are very useful starting materials for the synthesis of various bioactive molecules¹³⁻¹⁵. 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 design¹⁶⁻¹⁸. 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 reference¹³. 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-H₂O to give the title compounds 7. White crystal, yield 84.5 %, m.p. 175-176 °C; 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 $\times$ 0.16 mm $\times$ 0.12 mm was mounted on a Bruker SMART 1000 CCD area-detector diffractometer with a graphite-monochromated MoK α radiation ($\lambda = 0.71073$ Å) by using a Phi scan modes at 113(2) K in the range of $2.06^\circ \leq \theta \leq 25.02^\circ$. A total of 7491 reflections were collected, of which 3544 were independent ($R_{int} = 0.1576$) and 1776 were observed with $I > 2\sigma(I)$. The calculations were performed with SHELXS-97 program¹⁹ 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 $\Delta\rho_{\min} = -0.68 \text{ e } \text{\AA}^{-3}$. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-ray crystallography²⁰. A summary of the key crystallographic information were given in Table-1.

TABLE-1
CRYSTAL DATA OF THE TITLE COMPOUND

Empirical Formula	C ₉ H ₁₃ N ₃ OS
Formula weight	211.28
T/K	113(2)
λ/nm	0.071073
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 10.238(2) \text{ \AA}$ $\alpha = 104.09(3)^\circ$ $b = 10.325(2) \text{ \AA}$ $\beta = 109.50(3)^\circ$ $c = 10.560(2) \text{ \AA}$ $\gamma = 93.40(3)^\circ$
V/nm^3	$1008.4(3) \text{ \AA}^3$
Z	4
Calculated density/($\text{g}\cdot\text{cm}^{-3}$)	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 [$R_{\text{int}} = 0.1576$]
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0970$, $wR2 = 0.2147$
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 temperature¹³ (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 $\mu\text{g/mL}$ 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 ($\text{\AA}$) AND BOND ANGLES ($^\circ$)

Bond	Dist.	Angle	($^\circ$)
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 [$1.295(6) \text{ \AA}$] and C6 = N3 bond [$1.307(6) \text{ \AA}$] are similar with the general C=N double bond length of $1.27 \text{ \AA}$ ²¹⁻²³. The amide bond are normal, which is similar with the reported references²⁴⁻²⁷. As shown in Fig. 1, the 1,2,3-thiadiazole ring (N2, N3, S1, C5, C6) is fairly planar with mean deviation of $0.0035 \text{ \AA}$. 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				

ACKNOWLEDGEMENTS

The project was supported by the Program of National Natural Science Foundation of China (21102131). Thanks are also due to Dr. Liu for the crystal elucidation and culture.

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