Synthesis and Crystal Structure of Novel Ethyl 2-chloro-2-(4-(p-tolyl)-1,2,3-thiadiazol-5-yl)acetate

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(Received on 23rd May 2013, accepted in revised form 19th September 2013)

Summary: A new 1,2,3-thiadiazole compound was synthesized. The crystal structure of the title compound ($C_{13}H_{13}ClN_2O_2S$, Mr = 296.76) has been determined by single-crystal X-ray diffraction. The crystal is of triclinic, space group P-1 with a = 6.903(2), b = 9.875(3), c = 10.903(4) Å, α = 75.217(5) °, β = 79.698(5) °, γ = 80.788(5)°, V = 701.9(4)Å^3, Z = 2, F(000) = 308, Dc = 1.404 g/cm^3, μ = 0.42 mm^{-1}, the final R1 = 0.0324 and wR2 = 0.0823 for 2349 observed reflections with I > 2σ(I). A total of 4068 reflections were collected, of which 2842 were independent (R_{int} = 0.0146).

Keywords: Crystal structure, synthesis, 1,2,3-thiadiazole.

Introduction

In recent years, nitro and sulfur linked heterocyclic compounds had been research hotspot because of their biological importance [1-5]. 1,2,3-Thiadiazole compounds had been claimed to have beneficial medicinal and agricultural applications. Many 1,2,3-thiadiazole derivatives exhibited excellent biological activities, such as fungicidal activity [6-8], anti-HBV activity [9, 10], herbicidal activity [11, 12], antiamoebic activity [13] and so on. On the other hand, 1,2,3-thidiazole has been widely studied as they are useful intermediates in organic synthesis. For example, the plant inducers (thiadinal [14] and BTH [15]) were discovered (Figure **1**).

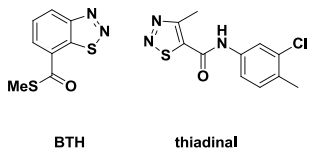

Fig. 1: The structural of BTH and thiadinal.

In view of the facts mentioned above, and also as a part of our work [16, 17] on the synthesis of heterocyclic compounds, the title compounds were synthesized. The single crystal structure of the title compound was determined by X-ray diffraction.

Results and Discussion

The selected bond lengths, bond angles are shown in Table **1**. The selected torsion angles are shown in Table **2**. The molecular structure of the title compound is shown in Figure **2**. The molecular packing of the molecule is shown in Figure **3**.

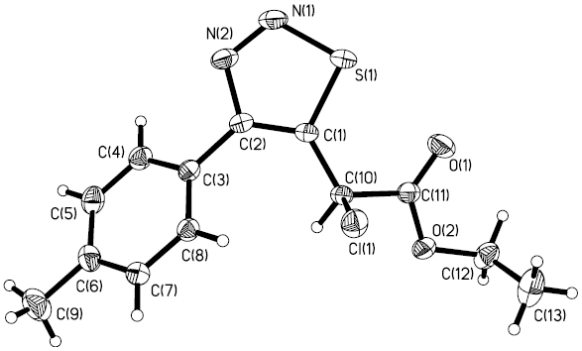

Fig. 2: Molecular structure of the title compound, showing displacement ellipsoids drawn at the 30% probability level.

From the Figure **2**, the absolute configuration of title compound was determined to be S on the basis of its single-crystal X-ray structure. Generally, the average bond lengths and bond angles of ring system (phenyl and 1,2,3-thiadiazole) are normal. The C-H bond lengths are in the range of 0.93-0.97Å. The observed C-O, C-S, C-Cl bond lengths [C11-O1 = 1.199(2) Å, C1-S1 = 1.6999(16) Å and C10-Cl1 = 1.8110(17) Å] are comparable with C-O, C-S and C-Cl bond lengths of the references [18,

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19]. However, the C2=N2 bond [1.376(2)Å] is longer than the general C=N double bond length of 1.28 Å [21, 22]. The C–C bond lengths of 1,2,3-thiadiazole group is 1.373(2) Å. The N–S bond lengths of 1,2,3-thiadiazole group is 1.6707(18) Å. In the phenyl ring, the C–C bond lengths range from 1.377(3) to 1.387(2) Å, almost equal to the values of typical bonds of aromatic structure [22-26]. The bond angles of phenyl ring vary from 117.86(17) to 122.28(15)° with the average of 120°. Also, the bond angles of 1,2,3-thiadiazole ring are from 92.88(8) to 113.77(15) °. The torsion angle of thioether group C(1)-C(10)-C(11)-O(1) is 27.6(3)°, which indicated that the C=O is nearly planar with the 1,2,3-thiadiazole ring.

Table-1: Selected Bond Lengths (Å) and Bond Angles (°).

Bond	Dist.	Angle	(°)
Cl(1)-C(10)	1.8110(17)	N(1)-S(1)-C(1)	92.88(8)
S(1)-N(1)	1.6707(18)	N(2)-N(1)-S(1)	112.05(12)
S(1)-C(1)	1.6999(16)	N(1)-N(2)-C(2)	113.77(15)
N(1)-N(2)	1.294(2)	C(11)-O(2)-C(12)	117.96(15)
N(2)-C(2)	1.376(2)	C(2)-C(1)-C(10)	128.00(15)
O(1)-C(11)	1.199(2)	C(2)-C(1)-S(1)	107.98(12)
O(2)-C(11)	1.315(2)	C(10)-C(1)-S(1)	124.02(13)
O(2)-C(12)	1.459(2)	C(1)-C(2)-N(2)	113.33(15)
C(1)-C(2)	1.373(2)	C(1)-C(2)-C(3)	129.22(15)
C(1)-C(10)	1.485(2)	N(2)-C(2)-C(3)	117.44(15)
C(2)-C(3)	1.476(2)	C(4)-C(3)-C(8)	118.40(16)
C(3)-C(4)	1.387(2)	C(4)-C(3)-C(2)	119.31(15)
C(3)-C(8)	1.390(2)	C(7)-C(8)-C(3)	120.62(16)
C(4)-C(5)	1.377(3)	C(1)-C(10)-C(11)	114.95(13)
C(5)-C(6)	1.386(3)	C(1)-C(10)-Cl(1)	109.83(11)
C(6)-C(7)	1.383(3)	C(11)-C(10)-Cl(1)	103.86(12)
C(6)-C(9)	1.509(3)	O(1)-C(11)-O(2)	125.84(17)
C(7)-C(8)	1.382(2)	O(1)-C(11)-C(10)	123.89(16)
C(10)-C(11)	1.516(2)	O(2)-C(11)-C(10)	110.24(14)

Table-2: Selected Torsion Angles (°).

Torsion angles	(°)	Torsion angles	(°)
C(1)-S(1)-N(1)-N(2)	-0.36(15)	C(4)-C(5)-C(6)-C(7)	0.2(3)
S(1)-N(1)-N(2)-C(2)	0.5(2)	C(4)-C(5)-C(6)-C(9)	-179.8(2)
N(1)-S(1)-C(1)-C(2)	0.15(14)	C(5)-C(6)-C(7)-C(8)	0.0(3)
N(1)-S(1)-C(1)-C(10)	-179.04(15)	C(9)-C(6)-C(7)-C(8)	180.0(2)
C(10)-C(1)-C(2)-N(2)	179.23(16)	C(6)-C(7)-C(8)-C(3)	-0.5(3)
S(1)-C(1)-C(2)-N(2)	0.07(19)	C(4)-C(3)-C(8)-C(7)	0.7(3)
C(10)-C(1)-C(2)-C(3)	-2.1(3)	C(2)-C(1)-C(10)-C(11)	154.32(17)
S(1)-C(1)-C(2)-C(3)	178.75(14)	S(1)-C(1)-C(10)-C(11)	-26.7(2)
N(1)-N(2)-C(2)-C(1)	-0.4(2)	C(2)-C(1)-C(10)-Cl(1)	-89.03(19)
N(1)-N(2)-C(2)-C(3)	-179.20(15)	S(1)-C(1)-C(10)-Cl(1)	90.00(15)
C(1)-C(2)-C(3)-C(4)	-143.05(19)	C(12)-O(2)-C(11)-O(1)	4.3(3)
N(2)-C(2)-C(3)-C(4)	35.6(2)	C(12)-O(2)-C(11)-C(10)	-173.75(15)
C(1)-C(2)-C(3)-C(8)	37.7(3)	C(1)-C(10)-C(11)-O(1)	27.6(3)
N(2)-C(2)-C(3)-C(8)	-143.69(17)	Cl(1)-C(10)-C(11)-O(1)	-92.4(2)
C(8)-C(3)-C(4)-C(5)	-0.5(3)	C(1)-C(10)-C(11)-O(2)	-154.32(15)
C(2)-C(3)-C(4)-C(5)	-179.81(17)	Cl(1)-C(10)-C(11)-O(2)	85.67(15)
C(3)-C(4)-C(5)-C(6)	0.1(3)	C(11)-O(2)-C(12)-C(13)	98.0(2)

As shown in Figure **2**, the 1,2,3-thiadiazole ring is nearly planar with phenyl ring with a quite small dihedral angle (θ) of 36.5°. The phenyl ring (C3, C4, C5, C6, C7, C8) and thiadiazole ring (N1, N2, S1, C1, C2) are fairly planar with plane equation -3.648x + 7.395y + 0.169z = 5.9671 and -0.551x + 8.134y + -3.510z = 4.2885 respectively, and the largest deviation from the least squares plane is 0.0018 nm and 0.0015 nm.

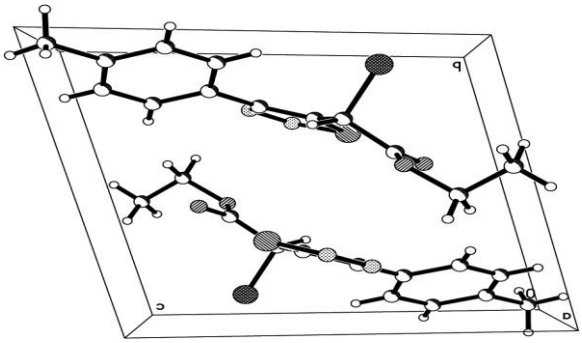


Fig. 3: The packing of title compound.

The intermolecular edge-to-face π-π stacking appears between the phenyl ring C3~C8 and the CH_2 in another adjacent molecule (Fig. **3**), in which the distance of H12B and the centroid of phenyl ring C3~C8 is 2.616 Å, with the angle of C8–H12B and the phenyl centroid being 89.53º. These interactions can help to further stabilize the crystal structure.

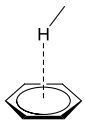
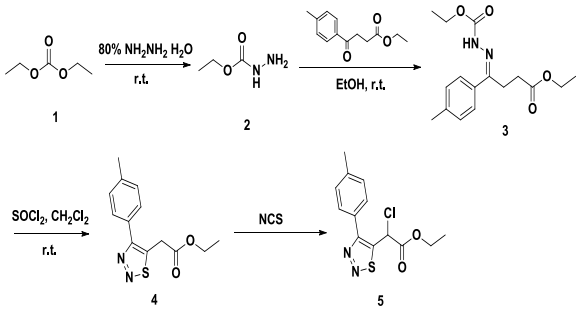


Fig. **3**: edge-to-face of π-π stacking.

Experimental

Synthesis

The title compounds were synthesized according to the route shown in Scheme **1**, and the yields were not optimized. Crystallographic data of the compound were collected on a Bruker SMART CCD1000 diffractometer. All the reagents are of analytical grade or freshly prepared before use.



Scheme-1: The synthetic route of title compound.

Carbonic acid diethyl ester (11.8 g, 0.1 mol) and hydrazine hydrate (5.6 mL, 0.095 mol, 85%) were added into a 250 mL round-bottom flask equipped with a condenser. The reaction mixture was heated to 50 ^{o}C and stirred for 20 min, and then cooled down to room temperature and further stirred for 30 h. Water, ethanol, and excess carbonic acid diethyl ester were distilled off under reduced pressure. After drying, a white crystal (**2**) (9.88 g) was obtained with a yield of 95%. To a stirred solution of compound 2 (6.36 g, 0.06 mol) in ethanol (16.7 mL), a solution of ethyl 4-oxo-4-(p-tolyl)butanoate (13.2 g, 0.06 mol) in ethanol (3.7 mL) was added at room temperature. Stirring was continued for 6 h. Then, the solvent was removed in vacuo and the crude product ethyl 2-(4-ethoxy-4-oxo-1-(p-tolyl)butylidene)hydrazineca rboxylate was directly used in the next step without further purification. Ethyl 2-(4-ethoxy-4-oxo-1-(p-tolyl)butylidene)hydrazineca rboxylate (18.36 g, 0.06 mol) was dissolved in dry dichloromethane (25 mL), and thionyl chloride (20 mL) was further added into the stirred reaction mixture dropwise at 0 ^{o}C for 1 h. Next, the reaction mixture was permitted to stand for 20 h at room temperature. The excess thionyl chloride and dichloromethane were distilled off, and the remaining residue was subjected to fractional distillation under reduced pressure. A slightly yellowish oil (**4**) (13.1 g) was obtained with a yield of 50%. To a solution of **4** (5.24 g, 20 mmol) in DMF (30 mL) was added the NCS (2.8 g, 21 mmol) and the mixture was stirred for 1 h at 100 °C, cooled to room temperature, left stand overnight, and then slowly poured into ice-water (100 mL) to precipitate a white solid. The solid was filtered and dried to obtain compound **5**. Yield 65%, m.p. 112-113 ◦C; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.52(t, *J* = 7.0 Hz, 3H, Me), 2.48(s, 3H, CH_3), 4.44(q, *J* = 7.1 Hz, 2H, CH_2), 5.70(s, 1H, CH), 7.43(d, *J* = 8.1 Hz, 2H, Ph), 7.74(d, *J* = 8.1 Hz, 2H, Ph).

Structure Determination

The cube-shaped single crystal of the title compound was obtained by recrystallization from EtOH. The crystal with dimensions of 0.26mm ×0.24mm × 0.20mm was mounted on a Rigaku Saturn diffractometer with a graphite-monochromated MoKα radiation (λ = 0.71073Å) by using a Phi scan modes at 293(2) K in the range of 2.15°≤θ≤26.40°. A total of 4068 reflections were collected, of which 2842 were independent (R_{int} = 0.0146) and 2349 were observed with I > 2σ(I). The calculations were performed with SHELXS-97 program [27] 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 R = 0.0324 and wR = 0.0823 ($w = 1/[s^2(F_o^2) + (0.0394P)^2 + 0.2015P]$ where $P = (F_o^2 + 2F_c^2)/3$), S = 1.04, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.21$ and $\Delta\rho_{min} = -0.22$ e Å^{-1}. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-Ray Crystallography [28]. A summary of the key crystallgraphic information are given in Table 3.

Table-3: Crystal Structure and Data Refinement Parameters.

Empirical Formula	$C_{13}H_{13}ClN_2O_2S$
Formula Weight	296.76
Crystal System / Space Group	Triclinic, P-1
a / Å	6.903(2)
b / Å	9.875(3)
c / Å	10.903(4)
α / °	75.217(5)
β / °	79.698(5)
γ / °	80.788(5)
V / Å^3	701.9(4)
Z	2
D $_{calc}$ (g/cm^3)	1.404
μ (mm^{-1})	0.4200
Crystal size (mm)	0.26 × 0.24 × 0.20
Color / Shape	Colorless/Cube
Temp (K)	293(2)
Theta range for collection	2.15 to 26.40°
Reflections collected	4068
Independent reflections	2842
Data/restraints/parameters	2842 / 0 / 174
Goodness of fit on F^2	1.045
Final R indices [I > 2σ(I)]	R1 = 0.0324, wR2 = 0.0823
R indices (all data)	R1 = 0.0427, wR2 = 0.0881
Largest difference peak/hole	0.211 and -0.219

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