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The synthesis and crystal structure of new 3,6-bis[1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazole

Heng-Shan Dong[(1)]* **and Bin Wang**[(2)]

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The 3,6-bis[1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazole was synthesized from *p*-ethoxyaniline to 8 with 1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-caroxylic acid. The yielded product 9 was investigated with X-ray crystallographic, NMR, MS, and IR techniques. Compound 9, $C_{25}H_{24}N_{10}O_2S$, Mr = 528.60, crystallizes in the triclinic space group $P\bar{1}$ with unit cell parameters $a = 6.4490(10)$, $b = 11.481(2)$, $c = 18.168(4)$ Å, $\alpha = 72.08(3)$, $\beta = 86.57(3)$, $\gamma = 86.72(3)^\circ$. $V = 1276.6(4)$ Å^3, $Z = 2$, Dx $= 1.375$ Mgm^{-3}. The final R was 0.0589.

KEY WORDS: Crystal structure; 1,2,3-triazole; *s*-triazolo[3,4-b]-1,3,4-thiadiazole; synthesis.

Introduction

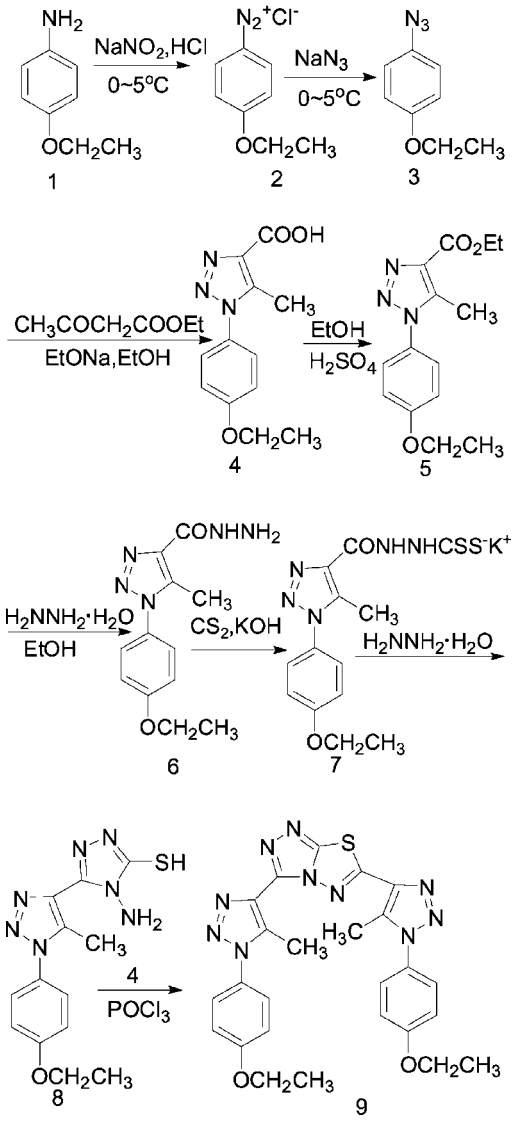
It is reported that the 1,3,4-triazole nucleus, 1,2,3-triazole nucleus, some new 1,3,4-triazole derivatives, and the 1,2,3-triazole derivatives possess multiformity biological and medication activities.[1] Likewise the 1,3,4-thiadiazole nucleus which incorporates an N—C—S linkage exhibits a large number of biological activities.[2] The fused 1,3,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives show various biological effects, such as antifungal,[3] antibacterial, and CNS depressant activities.[4] A triazolo-thiadiazole system may be viewed as a cyclic analog of two very important components—thiosemicarbazide and biguanide, which often display diverse biological activities. Therefore, it is worthwhile to investigate the system, combining these three biologically active components in a compact system for screening of their biologic activities.

We have reported the crystalline structure of 2-(3-bromoanilino)-5-[5-amino-1-(4-chlorophenyl)-1,2,3-triazole-4-yl]-1,3,4-thiodiazole and their derivatives.[4–6] Recently, we obtained a novel compound 3,6-bis[1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazole. The route of syntheses is in Scheme 1.

Experimental section

All melting points were uncorrected and determined on an XT_4-100x microscopic melting point apparatus. IR spectra were obtained in KBr discs on a Shimadzu IR-435 spectrometer. MS were performed on a HP-5988A spectrometer (EI

(1) National Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, Gansu 730000, P. R. China.
(2) College of Science and Engineering, Gansu Association University, Lanzhou, Gansu 730000, P. R. China.
*To whom correspondence should be addressed; e-mail: donghengshan@lzu.edu.cn.



Scheme 1

at 70 eV). ^{1}H NMR spectroscopy ($CDCl_3$) were recorded on Avance Mercury plus-300 instrument with TMS as an internal standard. Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer.

Phosphorus oxychloride was redistilled (bp 105).

1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-caroxylic acid 4 were prepared following methods in the literature.[7,8] Mp166–167°C.

Preparation of ethyl 1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-carboxyate 5 was following method in the literature.[1]

The yield of 5 (a white crystalline solid, mp 113–114°C) was 23.4 g (85.0%). ^{1}HNMR: 7.304–7.349 (d, 2H, $J = 9.0$ Hz, Ar_1-3,5), 7.000–7.045 (d, 2H, $J = 9.0$ Hz, Ar_1-2,6), 4.399–4.505 (q, 2H, $J = 7.0$ Hz, $TRZ_1CO_2CH_2$-), 4.042–4.146 (q, 2H, $J = 6.8$ Hz, Ar_1OCH_2-), 2.540 (s, 3H, TRZ_1-CH_3), 1.417–1.487 (t, 3H, $J = 7.0$ Hz, $TRZ_1CO_2CH_2C\underline{H}_3$), 1.402–1.472 (t, 3H, $J = 6.8$ Hz, Ar1$OCH_2C\underline{H}_3$). MS: 275($M^\dagger$, 45), 247(M-28 —N_2 or CH_2=CH_2, 1), 230(M-45— CH_3CH_2O, 10), 218(M-57 —N_2—CH_3CH_2,— 17), 202 (M—CH_3CH_2OCO, 10), 190(27), 174(58), 146(100), 121(10), 83(86), 65(68). IR: 3411, 3091, 2983, 2935, 2884, 1717, 1593, 1563, 1516, 1435, 1375, 1349, 1248, 1222, 1120, 1103, 1049, 1023, 983, 837, 786 cm^{-1}.

1-(4-Ethoxyphenyl)-5-methyl-1,2,3-triazol-4-carbonylhydrazine 6 was prepared from 5 following procedure method in the literature.[1]

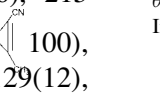
The yield of compound is 93.0%, mp 222–223°C. ^{1}HNMR: 7.477–7.521 (d, 2H, $J =$ 8.8 Hz, Ar_1-3,5), 7.095–7.139 (d, 2H, $J =$ 8.8 Hz, Ar_1-2,6), 4.450–4.720 (broad peak, 3H, —$NHNH_2$), 4.054–4.157 (q, 2H, $J = 7.0$ Hz, Ar_1OCH_2–), 2.474 (s, 3H, TRZ_1—CH_3), 1.315–1.385 (t, 3H, $J = 7.0$ Hz, $Ar_1OCH_2CH_3$). MS: 261($M^\dagger$, 72), 217(5), 204(42), 202(25), 174(49), 162(20), 146(86), 134(15), 121(16), 119(21), 83(31), 77(25), 69(50), 65(66), 57(77), 43(100). IR: 3307, 3264, 3213 (N—H), 2979, 2931, 1669 (C=O), 1639, 1608, 1587, 1516, 1476, 1447, 1269, 1249 (Are—O—R), 1119, 1045, 959 (1,2,3-triazole ring), 845, 658 cm^{-1}.

1-Amino-5-[1-(4-ethoxyphenyl)-2-mercapto-5-methyl-1,2,3-triazol-4-yl]-1,3,4-triazole 8 was prepared from 6 via 7 following the method reported in the literature.[1]

The compound 8 is white flak, 17.8 g (70% yield), mp 204–205°C. ^{1}HNMR: 7.371–7.400(d, 2H, $J = 8.7$ Hz, Ar_1-3,5), 7.047–7.076(d, 2H, $J = 8.7$ Hz, Ar_1-2,6), 4.080–4.150(q, 2H, $J =$ 7.0 Hz, Ar_1—OCH_2—), 2.525(s, 3H, TRZ_1—CH_3), 2.521(s, 1H, —SH), 1.620–1.840(broad peak,

2H, —NH_2), 1.449–1.497(t, 3H, $J = 7.0$ Hz, Ar_1—OCH_2CH_3). MS: 317($M^{\dagger}$, 16), 302(1), 285(1), 273(3), 260(5), 201(3), 194(17), 179(8), 173(3), 171(11), 151(11), 137(13), 121(100), 111(7), 105(23), 95(10), 83(10), 77(17), 69(16), 57(16), 55(20), 43(19). IR: 3449, 3281(N—H), 3186, 3111, 2974, 2942, 2838, 2783(S—H), 1632, 1610(C=N), 1519, 1499, 1467, 1291, 1254(Ar—O—R), 1174, 1019, 949(1,2,3-triazole ring), 840, 669.

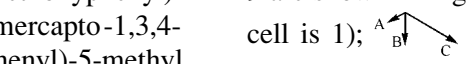
General procedure of preparation of 3,6-bis [1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-yl]-*s*-triazolo[3, 4- b]-1, 3, 4-thiadiazole derivatives 9.

A mixture of 1-amino-5-[1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-yl]-2-mercapto-1,3,4-triazole 8 (1 mmol). 1-(4-ethoxyphenyl)-5-methyl -1,2,3-triazol-4-caroxylic acid (1 mmol) and $POCl_3$ (5 mL) was heated under refluxing for 6 h with stirring. The cooled reaction mixture was poured into crushed ice and made alkaline by adding potassium hydroxide, and then the resulting solid was filtered and dried. The solid was purified by chromatography on a column of silica gel and eluted successively with 2:1 ethyl acetate–petroleum ether to give colorless block of Compound 9 Yield 72%, mp 226–227°C. ^{1}HNMR: 7.375–7.463 (2d, 4H, $J =$ 8.1 Hz, Ar_1, Ar_2-2,6), 7.046–7.097 (d, 4H, $J = 8.1$ Hz, Ar_1, Ar_2-3,5), 4.082–4.152 (2q, 4H, $J = 7.2$ Hz, Ar_1, Ar_2—OCH_2—), 2.726, 2.755 (2s, 6H, Ar_1, Ar_2—CH_3), 1.448–1.495 (t, 6H, $J = 7.2$ Hz, Ar_1, Ar_2—$OCCH_3$). MS M/z: 528($M^{\dagger}$, 1.7%), 500(M-28, —N_2 or CH_2=CH_2, 57), 471(M-28-28, 25), 443(M-28-28-28, 2), 313(3), 285(3), 257(7), 245(10), 228(6), 215 (18), 200(39), 186(11), 172(

100), 171(91), 159(12), 146(31), 137(14), 129(12), 123(17), 115(14), 111(27), 97(50), 91 (31), 83(57), 77(27), 71(56), 65(49), 57(75), 44(69). IR: 3067, 2981, 2920, 1608, 1584, 1516, 1462, 1303, 1255, 1172, 1115, 1045, 967, 947, 843, 782, 721.

The purified product was dissolved in chloroform, petroleum ether, and ethanol solvent. The crystal was obtained after 15 d by evaporation of the solvent.

Single crystals were selected and mounted on the tip of a glass fiber. Preliminary examination and data collection were performed with MoKα radiation($\lambda = 0.71073$ Å) on an Enraf-Nonius CAD4 computer controlled kappa axis diffractometer operating in the $\omega/2\theta$ scanning mode. The structure was determined by direct methods (SHELXS-86) and refined by full covariance matrix methods (SHELXL-97). The crystal data and the refinement details are given in Table 1.

The structure of the title compound is shown in Fig. 1. The unit cell parameters of the compound 9 are shown in Fig. 2 (The coordinate of the unit cell is 1); 

) The selected bond lengths are given in Table 2, selected bond angles

Table 1. Crystal Data and Structure Refinement Details

Empirical formula	$C_{25}H_{24}N_{10}O_2S$
CCDC deposit no	235478
Formula weight	528.60
Temperature, K	293(2)
Wavelength, Å	0.71073
Reflns. for cell determination	25
2θ range for above	10°–20°
Crystal system	triclinic
Space group	$P\bar{1}$
Cell dimensions	$a = 6.4490(10)$
	$b = 11.481(2)$
	$c = 18.168(4)$ Å
	$\alpha = 72.08(3)$
	$\beta = 86.57(3)$
	$\gamma = 86.72(3)°$
Volume, Å^3	1276.6(4)
Z	2
Density(calculated)	1.375 mg/m^3
Absorption coefficient	0.172 mμ^{-1}
$F(000)$	552.0
θ range for data collection	4.19°–21.26°
Index ranges	$0 \le h \le 6$;
	$-11 \le k \le 11$;
	$-18 \le l \le 18$
Reflections collected	2820
Independent reflection	1614
Data/Restrains/Parameters	2820/0/344
Goodness-of-fit on F^2	1.084
Final R indices [$I > \sigma 2(I)$]	$R_1 = 0.0589$,
	$wR_2 = 0.1401$
R indices	$R_1 = 0.1390$,
	$wR_2 = 0.1590$
Largest diff. Peak and hole	0.282 and −0.206 eÅ^{-3}

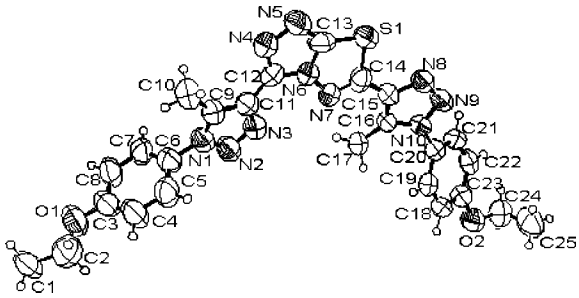


Fig. 1. ORTEP diagram of the compound 9 showing 50% thermal ellipsoids.

are given in Table 3. The geometric calculations were performed using the program SHELX-97.

Results and discussion

The structure of the title compound is shown in Fig. 1. In recent years the synthesis and characteristics of *s*-triazolo[3,4-b]-1,3,4-thiadiazoles have been investigated.[1] These heterocyclic compounds contain 1,2,4-triazole and 1,3,4-thiadiazole rings condensed through a C—N bond. In a continuation of our earlier studies,[4] we now report the crystal structure of 3,6-bis[1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazole 9.

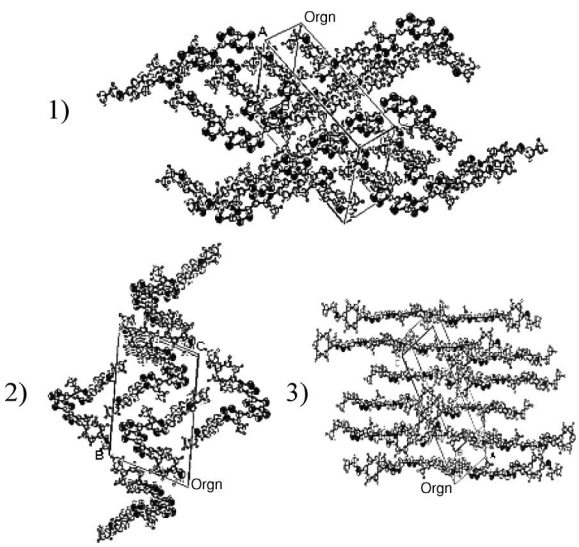


Fig. 2. The unit cell parameters of the compound 9.

Table 2. Selected Bond Lengths (Å)

Atoms	Length
S1—C13	1.734(12)
S1—C14	1.752(11)
O1—C3	1.328(13)
O1—C2	1.389(15)
O2—C23	1.366(12)
O2—C24	1.438(13)
N1—C9	1.339(12)
N1—N2	1.351(11)
N1—C6	1.435(13)
N2—N3	1.287(11)
N3—C11	1.327(12)
N4—C12	1.292(12)
N4—N5	1.406(11)
N5—C13	1.297(12)
N6—N7	1.341(10)
N6—C13	1.356(12)
N6—C12	1.381(11)
N7—C14	1.300(11)
N8—N9	1.284(10)
N8—C15	1.385(11)
N9—N10	1.381(10)
N10—C16	1.396(11)
N10—C20	1.401(11)
C1—C2	1.491(17)
C3—C4	1.358(15)
C3—C8	1.387(15)
C4—C5	1.398(16)
C5—C6	1.395(15)
C6—C7	1.340(14)
C7—C8	1.351(14)
C9—C11	1.371(13)
C9—C10	1.474(15)
C11—C12	1.457(14)
C14—C15	1.438(13)
C15—C16	1.340(12)
C16—C17	1.455(12)
C18—C19	1.343(13)
C18—C23	1.398(13)
C19—C20	1.377(12)
C20—C21	1.368(12)
C21—C22	1.355(13)
C22—C23	1.400(13)
C24—C25	1.409(16)

The bond lengths indicate a degree of delocalization around the ring system with the three C=N bonds ranging from N4—C12 1.292(12), N5—C13 1.297(12) to N7—C14 1.300(11)Å and

Table 3. Selected Bond Angles (°)

Atoms	Angle
C13—S1—C14	87.3(5)
C3—O1—C2	118.4(11)
C23—O2—C24	120.9(9)
C9—N1—N2	111.7(8)
C9—N1—C6	129.0(9)
N2—N1—C6	119.3(9)
N3—N2—N1	106.0(8)
N2—N3—C11	110.2(8)
C12—N4—N5	110.5(8)
C13—N5—N4	103.7(8)
N7—N6—C13	118.5(8)
N7—N6—C12	136.8(8)
C13—N6—C12	104.6(8)
C14—N7—N6	108.7(8)
N9—N8—C15	107.9(8)
N8—N9—N10	109.2(7)
N9—N10—C16	108.1(7)
N9—N10—C20	120.5(7)
C16—N10—C20	131.3(7)
O1—C2—C1	109.1(13)
O1—C3—C4	125.8(11)
O1—C3—C8	116.0(12)
C4—C3—C8	118.0(10)
C3—C4—C5	119.5(11)
C6—C5—C4	120.3(11)
C7—C6—C5	119.3(10)
C7—C6—N1	122.2(9)
C5—C6—N1	118.4(10)
C6—C7—C8	120.0(10)
C7—C8—C3	122.8(11)
N1—C9—C11	102.8(9)
N1—C9—C10	123.5(10)
C11—C9—C10	133.4(11)
N3—C11—C9	109.3(9)
N3—C11—C12	122.9(9)
C9—C11—C12	127.9(10)
N4—C12—N6	108.1(9)
N4—C12—C11	129.3(9)
N6—C12—C11	122.3(9)
N5—C13—N6	113.0(9)
N5—C13—S1	137.8(8)
N6—C13—S1	109.1(8)
N7—C14—C15	122.4(9)
N7—C14—S1	116.4(7)
C15—C14—S1	121.2(8)
C16—C15—N8	110.5(8)
C16—C15—C14	128.9(9)
N8—C15—C14	120.4(9)
C15—C16—N10	104.4(7)
C15—C16—C17	132.9(9)
N10—C16—C17	122.5(8)
C19—C18—C23	119.9(9)
C18—C19—C20	121.4(9)
C21—C20—C19	119.1(9)
C21—C20—N10	120.3(8)
C19—C20—N10	120.6(8)
C22—C21—C20	121.1(9)
C21—C22—C23	119.7(9)
O2—C23—C18	116.8(9)
O2—C23—C22	124.6(9)
C18—C23—C22	118.6(10)
C25—C24—O2	108.6(11)

the N—N bond lengths ranging from N6—N7 1.341(10) to N4—N5 1.406(11)Å.

The 1,2,3-triazole ring system is planar. The bond lengths N1—N2 1.351(11), N9—N10 1.381(10)Å, N2—N3 1.287(11), N8—N9 1.284(10)Å are in agreement with the values reported for triazole, N—N 1.352Å by Feneau-Dupont[9] and Huang.[10] The bond lengths C10—N3 1.359(6)Å and C9—N1 1.343(6)Å are between the bond lengths of C=N and C—N.

There aren't the strong interactions of hydrogen bond on the molecular stacking but weak intermolecular interaction of the pi–pi. The plane of 1,2,3-triazole ring, benzene ring, and fused 1,3,4-triazolo[3,4-b]-1,3,4-thiadiazole ring system is parallel to each other on intermolecular. It is shown in Fig. 2.

The dihedral angle (°) of 1,2,3-triazole and benzene ring plane is between 50 and 90, there isn't the conjugate of the pi–pi. The dihedral angle (°) of 1,2,3-triazole and fused 1,3,4-triazolo[3,4-b]-1,3,4-thiadiazole ring plane is between 165 and 180, there is the conjugate of the pi–pi.

Acknowledgments

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