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ORIGINAL PAPER

Structural Characterization of New Compound from the Ring-Opening Reaction of 3-(1H-1,2,4-triazol-1-yl)-1,5-Benzothiazepine with Phenylonitrile Oxide

Sheng-Qin Chen · Fei Ding · Yi-Chao Zhang · Fang-Ming Liu

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Abstract The crystal structure of the product (Z)-2-((Z)-((Z)-1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl)allylidene)amino) phenyl *N*-hydroxybenzimidothioate (**4**) was obtained by single crystal X-ray diffraction. The title compound, $C_{30}H_{23}N_5OS$ (**4**), crystallizes in the triclinic space group, P-1, with unit cell parameters a = 8.3306(17) Å, b = 11.394(2) Å, c = 14.560(3) Å, $\alpha = 78.75(3)^\circ$, $\beta = 89.96(3)^\circ$, $\gamma = 70.56(3)^\circ$, Z = 2. In the crystal structure, adjacent molecules are linked by O–H···N hydrogen bonds. H-bonds and π–π stacking are the main non-bonding interactions in the molecular structure and give support to molecular packing stability. In addition, the structure is supported by a weak intermolecular C–H···Cg π-ring interaction. Detail of the synthesis, structures, and spectroscopic properties of the title compound is discussed.

S.-Q. Chen · F.-M. Liu (✉)
College of Materials and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, People's Republic of China
e-mail: fmliu859@sohu.com

F. Ding
Technology Center of Juhua Group, Quzhou 324004, People's Republic of China

Y.-C. Zhang
WuXi PharmaTech Co., Ltd, Shanghai 200131, People's Republic of China

F.-M. Liu
College of Chemistry and Chemical Engineering, Xinjiang University, Urumqi 830046, People's Republic of China

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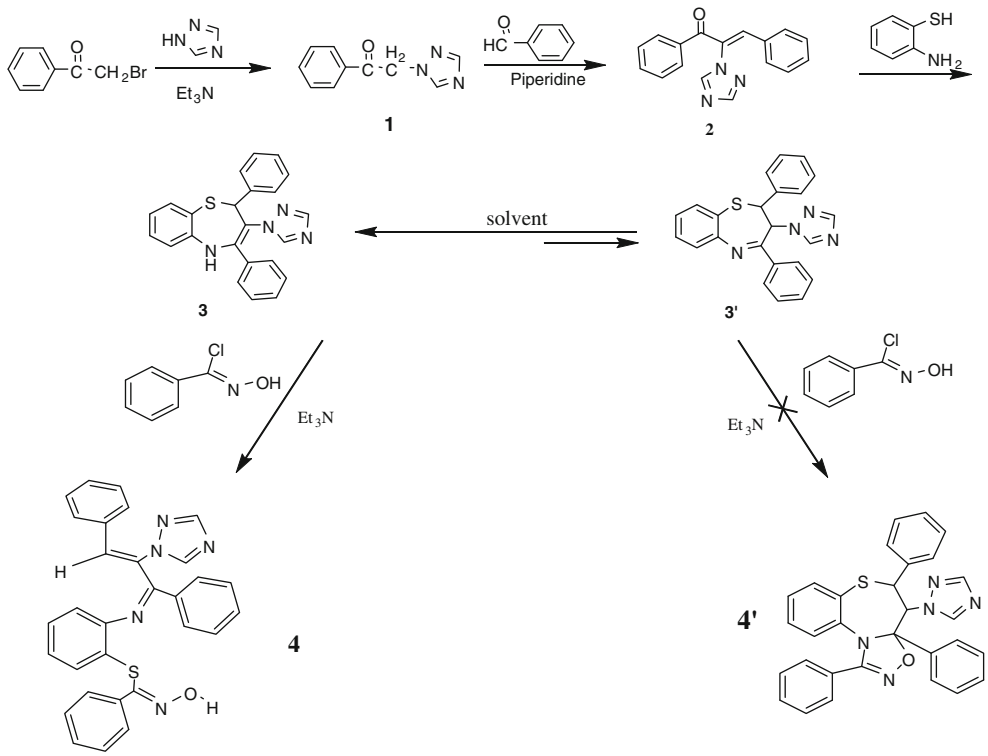
Introduction

Owing to their remarkable chemotherapeutic applications, 1,5-benzothiazepines [1–3] have been the object of intense investigation in medicinal chemistry and same of them are nowadays among the most widely used drugs in the treatment of cardiovascular disorders, such as Diltiazem [4],Thiazesim [5], and Clentiazem[6], etc. On account of this, a great deal of work has been done on the synthesis of 1,5-benzothiazepine derivatives aimed at defining its biochemical and pharmacological role [7–10]. Recently, annulated 1,5-benzothiazepine derivatives have attracted increasing attention with consideration that the addition of a third ring to bond [d] may be expected to enhance the activilty or modify the activity profile [11–14]. In addition, 1,2,4-triazole derivatives represent one of the most interesting and important classes of compounds, possessing a widespread biological activities such as antimicrobial and antifungal activities [15–19]. Many triazole derivatives, for example, fluconazole and itraconazole, have been commercially available antifungal agents [20, 21]. Meanwhile, the introduction of 1,2,4-triazole moiety into the parent compounds may improve the properties and biological activities of the compounds, it is therefore thought of interest to combine these two potential biologically active units into a single molecule for evaluating their biological activity.

A literature survey shows that 1,5-benzothiazepines with a 1,2,4-triazole moiety substituted at 3-position have never been reported so far. Taking into consideration of the important biological activity of 1,5-benzothiazepine and



Scheme 1 The synthesis of title compound

1,2,4-triazole moieties, as an extension of our investigations on the synthesis of new 1,5-benzothiazepine derivatives [22, 23], it is reported here the synthesis of a new compound of 1,5-benzothiazepine with a 1,2,4-triazole moiety substituted at 3-position and its reaction with phenylonitrile oxide, expecting to get the desired normal cycloadduct (**4′**) Scheme 1. Unfortunately, we only obtained the ring-opening product (**4**). The crystal structure of the molecular (**4**) was first determined by single-crystal X-ray diffraction (Fig. 1).

Experimental

Reagents and Apparatus

All reagents were of commercial availability. Melting points were measured on a mettler FP-5 capillary melting point apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The IR spectra were determined as potassium bromide pellet on a Bruker Equinox 55 FT-IR spectrophotometer. The [1] H-NMR spectra were recorded on a Varian Inova-400 spectrophotometer using TMS as an internal standard. EI-ms spectra were recorded with an Agilent 5975 apparatus. X-ray crystal structure was obtained using R-AXIS SPIDER X-ray diffraction.The starting compounds **1**, **2** were prepared according to the previously reported procedures [24, 25].

The Synthesis of 1,5-benzothiazepine Containing 1,2,4-triazole (3)

To a solution of chalcone (**2**) (4.0 mmol) in methanol (60 ml) was added o-aminothiophenol (4.0 mmol). The reaction mixture was kept under stirring at room temperature for 0.5 h.The mixture was heated under reflux for 20–30 min and then added CF_3COOH (1.2 ml). The refluxing was continued for 5–6 h. About half of the solvent was distilled off and the resulting mixture was allowed to stand at room temperature. The crystalline solid product thus separated by filtered, washed by cold methanol (2–3 mL) and dried. The crude compound was recrystallized from methanol.

3: White crystal, Yield 72.7%. m.p.209–211 °C. 1H-NMR (CDCl3, 400 MHz) δ: 8.00–6.70 (m, 16H), 6.10(m,0.5H), 5.88–5.85 (d, J = 12.0 Hz, 0.5H), 5.55–5.52 (d, J = 12.0 Hz, 0.5H), 5.43 (m,0.5H); IR (KBr): 3244, 3050, 1672, 1587, 1475, 699 cm^{-1}; MS (70 eV) m/z (%): 382 (M +), 313, 212 (100), 109, 65, 51; Anal.Calcd. for C23H18N4S: C, 72.22; H, 4.74; N, 14.65; Found C, 72.04; H, 4.817; N, 14.57.

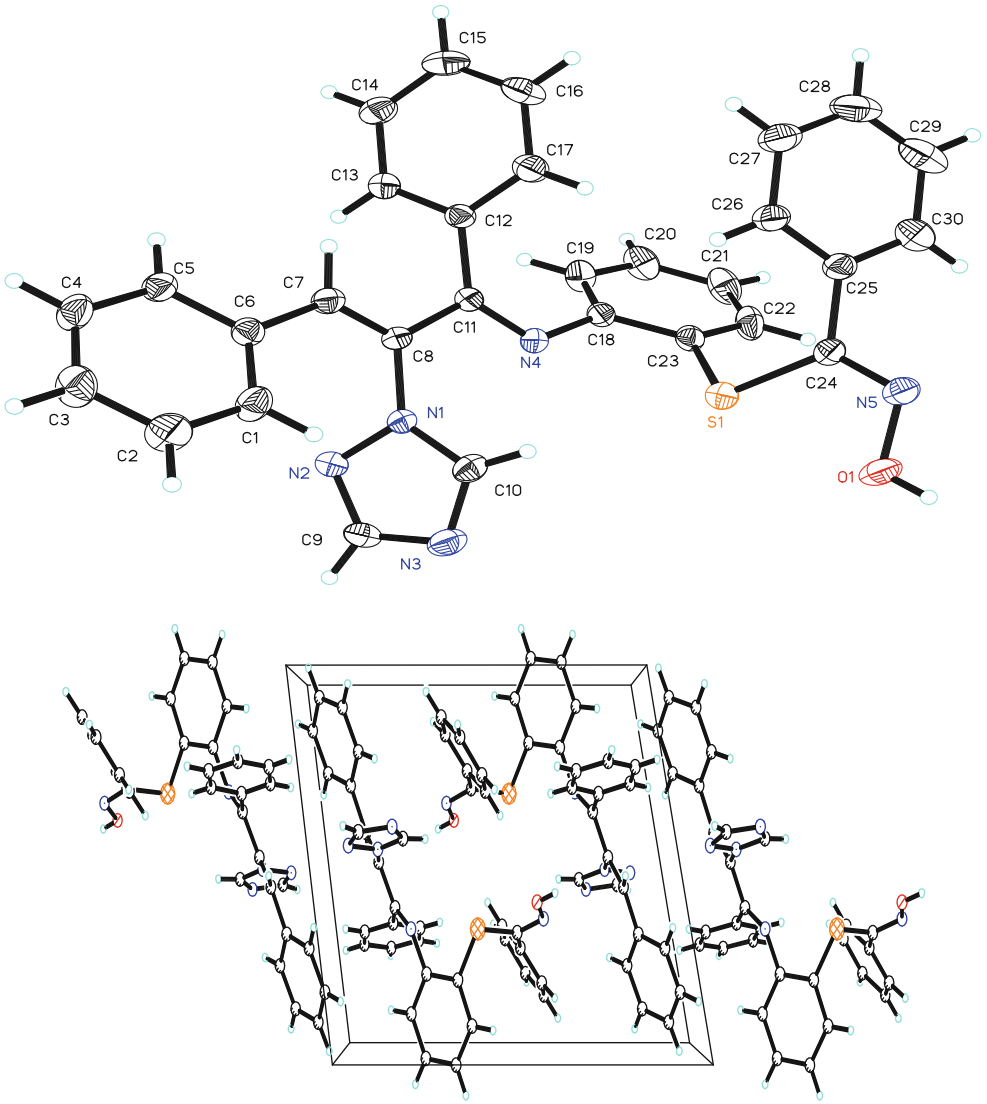


Fig. 1 ORTEP view and packing diagram of molecular structure of the title compound with 50% thermal ellipsoids. Dashed lines indicate hydrogen bonds

The Synthesis of (Z)-2-((Z)-((Z)-1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl)allylidene)amino)phenyl *N*-hydroxybenzimidothioate (4)

Benzohydroximinoyl chloride (1.5 mmol) was added under stirring to a solution of appropriate (E)-2,4-diphenyl-3-(1H-1,2,4-triazol-1-yl)-2,5-dihydrobenzo[b] [1, 4] thiazepine **3** (1 mmol) in methylene chloride (30 ml) and a solution of triethylamine (1.5 mmol) in the same solvent (5 ml) was added dropwise slowly. The reaction mixture was kept under magnetic stirring at room temperature for 4 days. After the completion of the reaction, the solvent was evaporated off at reduced pressure, and ether was added and the triethylamine hydrochloride was filtered. After removal of the solvent, the residue was purified by silica gel column chromatography with ethyl acetate/light petroleum (V:V = 1:5). A yellow crystal **4** cultured from methanol.

4: Yellow crystal, Yield 27.3%. m.p.203–205 °C. 1HNMR (CDCl3, 400 MHz) δ 6.15(1H,s); 8.59(1H,s);7.97, 8.28 (2H,2 s), 6.53–7.61 (19H,m) IR (KBr): 3384, 2360, 1635,1586, 1352, 761 cm^{-1}; MS (70 eV) m/z (%): 501 (M +), 432, 382, 313, 212 (100), 109, 77, 51; Anal. Calcd. for C30H23N5OS: C,71.83; H,4.62; N,13.96; Found C, 71.83; H, 4.613; N, 13.97.

X-ray Crystallography

The X-ray diffraction data of the single crystal **4** was collected on a crystal of approximate dimensions 0.540 × 0.240 × 0.180 mm by using Rigaku R-axis Spider diffractometer with graphite-monochromated MoKα radiation. All

Table 1 Summary of structure determination of compounds **4**

CCDC deposition number	**771603**
Formula	C30 H23 N5 O S
Formula weight	501.59
Crystal size (mm)	0.54 × 0.24 × 0.18
Temperature (K)	288(2)
Crystal colour	Yellow
Crystal system	Triclinic
Space group	P−1
Unit cell dimensions [A°] and angles (°)	
a (Å)	8.3306 (17)
b (Å)	11.394 (2)
c (Å)	14.560 (3)
α (°)	78.75 (3)
β (°)	89.96 (3)
γ (°)	70.56 (3)
Volume ($Å^3$)	1275.2 (4)
Z	2
Density (calculated) (Mg/m^3)	1.306
Absorption coefficient (mm^{-1})	0.160
F(000)	524
Theta range for data collection	3.05−27.47°
Index ranges	−10 <=h <=10, −14 <=k <=14, −18 <=l <=18
Reflections collected/unique	12128/5624
R(int)	0.0370
Refinement method	Full-matrix least-squares on F^2
Goodness of fit ref	1.022
Final *R* indices [I > 2.0 σ(I)]	$R1 = 0.0569$, $wR2 = 0.1177$
R indices (all data)	$R1 = 0.0956$, $wR2 = 0.1397$
Largest diff. Pesk and hole	0.198 and −0.271 e.A^−3

calculation was carried out on a computer with the aid of the SHELX-97 [26] and PLATON [27], program and refinements on F^2 were performed by full-matrix least-squares techniques with anisotropic displacement parameters for the non-hydrogen atoms. A summary of the crystallographic data and detail of the structure refinement are listed in Table 1.

CCDC 771603 for the corresponding compound of **4** contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from Cambridge Crystallographic Data Centre (CCDC)12 Union Road, Cambridge CB2 1EZ, UK; phone: + 44(0)1223-336408; fax: + 44(0)1223-336033; email: deposit@ccdc.cam.ac.uk;http://www.ccdc.cam.ac.uk.

Results and Discussion

The structure of the crystal **4** is displayed in Fig. 1. The bond length in this compound of C(6)–C(7), 1.467(3) Å; C(11)–C(12), 1.497(3) Å; C(8)–C(11), 1.478(3) Å; C(24)–C(25), 1.483(3) Å; N(1)–C(8), 1.434(3) Å; N(4)–C(18), 1.413(3) Å and C(7)–C(8), 1.335(3) Å; C(11)–N(4), 1.285(3) Å; C(24)–N(5), 1.280(3) Å, indicates it is a double bond between C(7) and C(8), C(11) and N(4) as well as N(5) and C(24) (Table 2). Besides, the molecule adopts a cis configuration about the central C=C and two C=N bonds. The four atoms of S1, C24, N5, O1 and C7, C8, C11, N4 are nearly coplanar, with its mean deviation from plane being 0.0069 and 0.0523 Å, respectively. Furthermore, the structure is characterized by the torsion angles: C(6)–C(7)–C(8)–N(1): 2.0(4), N(1)–C(8)–C(11)–N(4): −9.6(3), C(18)–N(4)–C(11)–C(12): −6.7(4) (Table 2).

Table 2 Selected bond lengths (Å), bond angles (°), and torsion angles (°) for compound **4**

Compound **4** (bond lengths (Å))	
N(1)–C(8)	1.434 (3)
N(4)–C(11)	1.285 (3)
N(4)–C(18)	1.413 (3)
N(5)–C(24)	1.280 (3)
C(6)–C(7)	1.467 (3)
C(7)–C(8)	1.335 (3)
C(8)–C(11)	1.478 (3)
C(11)–C(12)	1.497 (3)
C(24)–C(25)	1.483 (3)
O(1)–N(5)	1.394 (3)
S(1)–C(24)	1.772 (2)
S(1)–C(23)	1.779 (3)
Compound **4** (bond angles (°))	
N(5)–O(1)–H(1A)	109.5
C(24)–S(1)–C(23)	101.69 (11)
C(11)–N(4)–C(18)	124.04 (19)
C(24)–N(5)–O(1)	111.4 (2)
N(1)–C(8)–C(11)	115.83 (17)
N(4)–C(11)–C(8)	116.46 (19)
C(8)–C(11)–C(12)	117.54 (18)
C(19)–C(18)–N(4)	123.0 (2)
C(18)–C(23)–S(1)	119.18 (18)
N(5)–C(24)–C(25)	117.2 (2)
N(5)–C(24)–S(1)	122.18 (19)
C(25)–C(24)–S(1)	120.44 (16)
Compound **4** (torsion angles (°))	
C(6)–C(7)–C(8)–N(1)	2.0 (4)
C(18)–N(4)–C(11)–C(12)	−6.7 (4)
N(1)–C(8)–C(11)–N(4)	−9.6 (3)
C(18)–N(4)–C(11)–C(8)	176.8 (2)
C(7)–C(8)–C(11)–N(4)	169.2 (2)
C(7)–C(8)–C(11)–C(12)	−7.6 (3)
S(1)–C(24)–C(25)–C(30)	−130.2 (2)
C(23)–S(1)–C(24)–C(25)	37.2 (2)

Table 3 Intermolecular interactions (Å) in the compound **4**

D–Hf···A	D–H	H···A	D···A	D–H···A
O(1)–H(1A)···N(3)[i]	0.82	2.01	2.800 (3)	161
C(1)–H(1B)···N(1)	0.93	2.55	3.042 (3)	113

[i] 2−x, 1−y, 1−z

The dihedral angle between the plane (C7–C8–C11–N4) and the benzene ring plane (C1–C6) is 140.5°; the benzene ring plane (C12–C17) is 118.2°; the benzene ring plane (C18–C23) is 128.2°, the benzene ring plane (C25–C30) is 14.4°; the plane (S1-C24–N5–O1) is 116.4°,while the triazole ring plane and the plane (C7–C8–C11–N4) is 117.5°.

As seen from Fig. 1, the packing in this compound is held together by O–H···N, C–H···N hydrogen bonds and three C–H···Cg (π-Ring) (Table 3). In addition, the existence of weak π–π stacking interaction is observed between triazole and benzene ring (C12–C17). The distance between the centrality of interacting ring is Cg (1)···Cg (3) = 3.9185(17) Å (1 + x, y, z). [Cg (1) = center of gravity of the 1,2,4-triazole ring; Cg (3) = center of gravity of the benzene ring (C12–C17)].The existence of H-bonding and weak π–π stacking interaction in the molecular structure is great helpful to stabilize the crystal packing.

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