Synthesis, spectroscopy and crystal structure of 2-cyclohexyl-5-formyl-6-(4-bromophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole

Noor Shahina Begum[a]*, D.E. Vasundhara[a], G.D. Kolavi[b], K.V. Arjun Gowda[b] and I.M. Khazi[b]

[a]*Department of Studies in Chemistry, Bangalore University, Central College Campus, Bangalore 560 001, India*

[b]*Department of Chemistry, Karnatak University, Dharwad 580 003, India*

The preparation of 2-cyclohexyl-5-formyl-6-(4-bromophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (**3**) is described and its crystal structure is determined and discussed.

Keywords: fused midazoles, 1,3,4-thiadiazoles, crystal structure, Vilsmeier–Haack

The 1,3,4-thiadiazole nucleus is associated with a broad spectrum of biological activity, possibly due to the pharmacophoric isothioamide (S–C=N–) unit[1,2] present in the molecule. Secondly, the thiadiazole ring is bioisosteric with the thiazole moiety of the novel broad spectrum anthelmintic Tetramisole.[3,4] This fact, coupled with the reported anti-cancer properties of some thiadiazoles,[5] makes 1,3,4-thiadiazole derivatives compounds with potential pharmaceutical prospects.

Many imidazothiadiazole derivatives have been reported to possess diverse medicinal properties such as anthelmintic,[6] antimicrobial,[7] anti-inflammatory, antipyretic-analgesic properties[8] and many other activities of therapeutic significance.[9,10] These findings prompted us to synthesise the title compound so that it could be screened for its pharmacological activities, and to carry out its crystallographic structure elucidation. The title compound will be a good intermediate to synthesise various candidate compounds for pharmacological testing.

Results and discussion

Compound **3** was prepared in a straightforward fashion, by reaction of the amino-thiadiazole **1** with *p*-bromophenacyl bromide, followed by Vilsmeier–Haack formylation of **2**, as outlined in Scheme 1.

The crystal structure determination of compound **3** showed the bond distances and angles as given in Tables 1 and 2. The ORTEP diagram of the molecule is shown in Fig. 1.

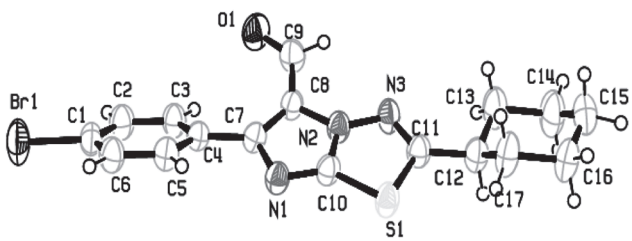
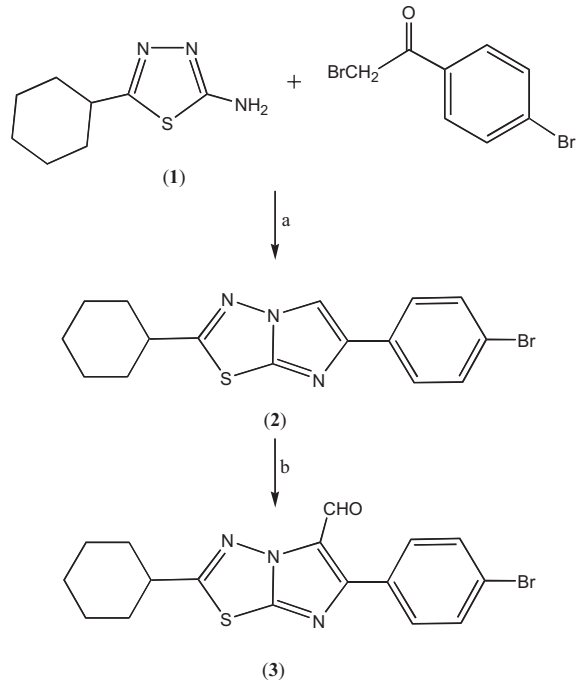


Fig. 1 ORTEP diagram of compound **3.**

Table 1 Selected bond lengths in compound **3**

bond	length (Å)	bond	length (Å)
Br(1)–C(1)	1.889(3)	C(4)–C(7)	1.463(4)
S(1)–C(10)	1.720(3)	C(8)–C(7)	1.399(4)
S(1)–C(11)	1.760(3)	C(8)–C(9)	1.438(4)
N(2)–C(10)	1.346(3)	C(11)–C(12)	1.497(4)
N(2)–N(3)	1.369(3)	C(12)–C(17)	1.494(5)
N(2)–C(8)	1.391(3)	C(12)–C(13)	1.502(4)
N(1)–C(10)	1.320(4)	C(16)–C(15)	1.487(6)
N(1)–C(7)	1.378(3)	C(16)–C(17)	1.523(4)
O(1)–C(9)	1.201(4	C(14)–C(15)	1.495(6)
N(3)–C(11)	1.295(4)	C(14)–C(13)	1.520(5)

* Correspondent. E-mail: noorsb@rediffmail.com



Scheme 1 *Reagents:* a, heat in EtOH; $NaHCO_3/H_2O$ b, DMF/$POCl_3$; Na_2CO_3/H_2O.

In the molecule, the imidazo-thiadiazole and bromophenyl rings are non-coplanar, being inclined at an angle of 27.344(29)° to each other. The normal to the formyl group plane is tilted *ca* 5° from that of the imidazo-thiadiazole ring. The formyl group is *cis* to the bromophenyl group. The dihedral angle between the two least square planes containing the formyl and bromophenyl groups is 33.852(8)°. Also, the cyclohexyl ring is found to be in the chair

Table 2 Selected bond angles in compound **3**

bonds	angle (º)	bonds	angle (º)
C(10)–S(1)–C(11)	87.96(14)	N(1)–C(7)–C(8)	111.5(2)
C(10)–N(2)–N(3)	118.9(2)	N(1)–C(7)–C(4)	118.9(2)
C(10)–N(2)–C(8)	108.2(2)	C(8)–C(7)–C(4)	129.6(2)
N(3)–N(2)–C(8)	132.8(2)	O(1)–C(9)–C(8)	126.4(3)
C(10)–N(1)–C(7)	104.3(2)	N(3)–C(11)–C(12)	124.0(3)
C(11)–N(3)–N(2)	107.8(2)	N(3)–C(11)–S(1)	116.2(2)
C(2)–C(1)–Br(1)	119.6(2)	C(12)–C(11)–S(1)	119.8(2)
C(6)–C(1)–Br(1)	118.7(2)	C(17)–C(12)–C(11)	112.4(3)
C(5)–C(4)–C(7)	118.9(2)	C(17)–C(12)–C(13)	111.7(3)
C(3)–C(4)–C(7)	122.7(2)	C(11)–C(12)–C(13)	112.1(3)
N(1)–C(10)–N(2)	112.9(2)	C(15)–C(16)–C(17)	112.4(3)
N(1)–C(10)–S(1)	138.1(2)	C(15)–C(14)–C(13)	112.6(3)
N(2)–C(10)–S(1)	109.0(2)	C(12)–C(13)–C(14)	111.4(3)
N(2)–C(8)–C(7)	103.1(2)	C(12)–C(17)–C(16)	111.8(3)
N(2)–C(8)–C(9)	119.6(2)	C(16)–C(15)–C(14	112.6(3)
C(7)–C(8)–C(9)	136.8(2)		

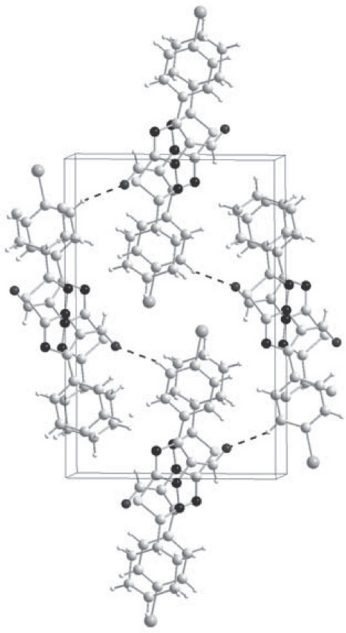


Fig. 2 View down the a axis, showing the C–H…O interactions.

conformation, since the bond angles in it are all nearly ideally tetrahedral showing that ring strain is negligible owing to puckering. The molecules are linked in chains through C–H···O hydrogen bond interactions (Fig. 2)**.** For the intermolecular C(6)–H(6)···O(1') bonding the following geometry is found: C–H 0.93 Å, H···O 2.39 Å, C···O 3.27 Å; C–H···O angle 159°.

The authors have earlier worked with imidazo[2,1-*b*][1,3,4] thiadiazoles containing pharmacophoric substituents.[11-13] The structural features, namely the angular orientation of imidazothiadiazole ring system with respect to other rings in the molecule as well as the C–H···O hydrogen bond aided self assembly are found to be common in all of them. Structural comparisons of all these compounds seem to point towards a unique binding mode to proteins in biological systems, which necessitate the virtual screening of these entities via docking studies.

Experimental

Melting points were determined in open capillaries. The IR spectra of samples as KBr pellets were recorded on a Nicolet FT IR Spectrometer (model 410, USA). NMR spectra in $CDCl_3$ were recorded on a Bruker 300 MHz Spectrometer (Model RX-300, Switzerland) using TMS as an internal standard. C, H and N analyses were carried out on a Thermoquest CHN analyser (Carlo Erba, Italy).

Compounds **1**, m.p. 246–248°C (lit.[14] m.p. 243–245°C) and **2**, m.p**.** 107–110°C (lit.[15] m.p.108–109°C) were prepared by literature procedures.

2-Cyclohexyl-5-formyl-6-(4-bromophenyl)imidazo[2,1-b][1,3,4] thiadiazole (**3**): Vilsmeier Haack reagent was prepared by adding $POCl_3$ (3 ml) to cold DMF (20 ml). Then 2-cyclohexyl-6-(4-bromophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (3.2 g, 8.84 mmol) was added to the reagent and the resulting solution was stirred at 0°C for 30 min. Stirring was continued for 2 h at room temperature, followed by further stirring for 2 h at 60°C. The reaction mixture was poured into cold 10% aqueous Na_2CO_3 and stirred at 90°C for 2 h. After cooling, the solution was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to provide the product **3** (2.43 g, 70%). The crystals for X-ray were obtained as colourless cubes, m.p. 144–146°C by slow evaporation of a solution of **3** in chloroform. IR (KBr): ν_{max} 2848, 1676, 1588 cm^{-1}. NMR ($CDCl_3$): δ 1.30–2.18 (m, 10H), 3.13 (m, 1H), 7.60 (d, J = 9 Hz, 2H), 7.77 (d, J = 9 Hz, 2H), 10.03 (s, 1H) ^{13}C NMR ($CDCl_3$) δ,25.9, 26.0, 33.0, 41.7, 109.5, 123.1, 126.9, 132.1, 133.4, 145.7, 170.5 and 177.5; Anal calcd for $C_{17}H_{16}BrN_3OS$: C, 52.31; H, 4.13; N, 10.77%. Found: C, 52.71; H, 4.27; N, 11.20%.

Crystal structure determination of **3**

The X-ray diffraction data were collected on a Bruker Smart CCD Area Detector System using MoKa (0.71073Å) radiation for the crystal. Intensity data were collected up to a maximum of 27.26° for the compound in the ω–ϕ scan mode. The data were processed using SAINTPLUS.[16] A total of 12,499 reflections were collected, resulting in 3360 (R_{int} = 0.023) independent reflections of which the number of reflections satisfying I>2 σ(I) criteria were 2538. These were treated as observed. The structure was solved by direct methods and difference Fourier synthesis using SHELXS97.[17] The positions and anisotropic displacement parameters of all non–Hydrogen atoms were included in the full matrix least-square refinement using SHELXL97.[18] Then the hydrogen atoms were fixed geometrically and were refined isotropically. The R indices for all data were R_1 = 0.0597 and wR_2 = 0.1173. The R factor for 'observed' data finally converged to 0.0427 with wR_2 = 0.1078. The maximum and minimum values of residual electron density were 0.711 and –0.661 $eÅ^{-3}$. Molecular diagrams were generated using ORTEP.[19]

Supplementary material

Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallography Data Centre. The deposition number is 671066.

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