Synthesis, spectroscopy and crystal structure of 2-ethyl-6-(4-nitrophenyl) imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde

Noor Shahina Begum[a]*, D.E. Vasundhara[a], C.R. Girija[a], G.D. Kolavi[b], V.S. Hegde[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-ethyl-6-(4-nitrophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (**4**) is described and its crystal structure is determined and discussed.

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

Imidazo[2,1-*b*][1,3,4]thiadiazoles are known for their promising biological and pharmacological activities.[1,2] Much interest has also been focused on the chemistry, anticonvulsant, analgesic[3] and antibacterial[4] activities displayed by compounds incorporating this heterocyclic system. In view of the pharmacological significance of the imidazo[2,1-*b*][1,3,4]thiadiazole ring system, it was considered worthwhile to synthesise its derivatives with pharmacophoric substituents, which may have equally significant roles to play in biological systems. The title compound is one of the members of this series. Also, 1,3,4-thiadiazole is bioisosteric with thiazole in Tetramizole,[5] which is a novel broad spectrum antihelmintic.

The compound was synthesised by Vilsmeier–Haack formylation of an imidazo[2,1–*b*][1,3,4]thiadiazole containing ethyl and nitrophenyl substituents (Scheme 1). The product was subjected to spectroscopic analysis using IR and ^{1}H and ^{13}C NMR techniques to confirm the presence of the ring system, and the site of formylation.

A single crystal X-ray diffraction analysis was carried out on compound **4** to investigate its supramolecular structure in terms of C–H···O hydrogen bonding. The analysis revealed certain interesting features such as the planarity of the molecule due to the co-planarity of the carbaldehyde group with the imidazo–thiadiazole ring, the presence of a strong intramolecular hydrogen bond, and the conformational rigidity of the pseudo seven-membered ring which contains it. The stabilisation of the structure due to intramolecular C–H···O and C–H···N interactions was analysed, leading to the conclusion that the supramolecular aggregation in the molecule was chiefly a function of C–H···O tetrameric units and C–H···N interactions.

Experimental

The melting points were determined in open capillaries. The IR spectra were recorded as KBr discs using a Nicolet FT-IR 410 spectrophotometre. ^{1}H NMR spectra were recorded on a Varian RXZ-300 MHz spectrometre using TMS as internal reference compound. C, H and N analyses were measured on a Heraus CHN rapid analyser at Karnatak University, Dharwad, India.

2-Ethyl-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (**4**): The title compound was prepared in two stages as shown in Scheme 1. 2-Ethyl-6-(4-nitrophenyl)imidazo[2,1-*b*][1,3,4] thiadiazole (**3**) was prepared by refluxing a mixture of *p*-nitrophenacyl bromide (**2**)[6] (2.44 g, 0.01 mol) and 2-amino-5-ethyl-1,3,4-thiadiazole (**1**)[7] (1.29 g, 0.01 mol) in absolute ethanol for 8 h. Solvent was distilled off and the solid hydrobromide that separated was collected by filtration, suspended in water and neutralised with aqueous sodium carbonate to get the free base. This was filtered off, washed with water, dried, and recrystallised from ethanol, providing compound **3** as a pale yellow crystalline solid (yield 62 %), m.p. 178–180 °C.

Compound **3**: IR (KBr): 2944 (ν_{C-H} aliph), 1602($\nu_{C=N}$), 1536, 1510, 1472, 1355 (ν_{NO2}), 1185, 1110, 1056, 861, 852, 748, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.46 (t, J = 3.3 Hz, 3H, CH_3), 3.04 (q, J = 3.3 Hz, 2H, CH_2), 7.96 (d, J = 8.7 Hz, 2H, C_2, C_6–H phenyl), 8.08 (s, 1H, C_5–H, imidazole), 8.23 (d, J = 8.7 Hz, 2H, C_3, C5–H, phenyl). ^{13}C NMR ($CDCl_3$): δ 13.2, 28.0, 122.1, 125.3, 130.1 137.6, 147.8, 151.2, 152.5, 169.9. Anal. Calcd for $C_{12}H_{10}N_4O_2S$; C, 52.54; H, 3.67; N, 20.43. Found: C, 52.44, H, 3.60, N, 20.38 %.

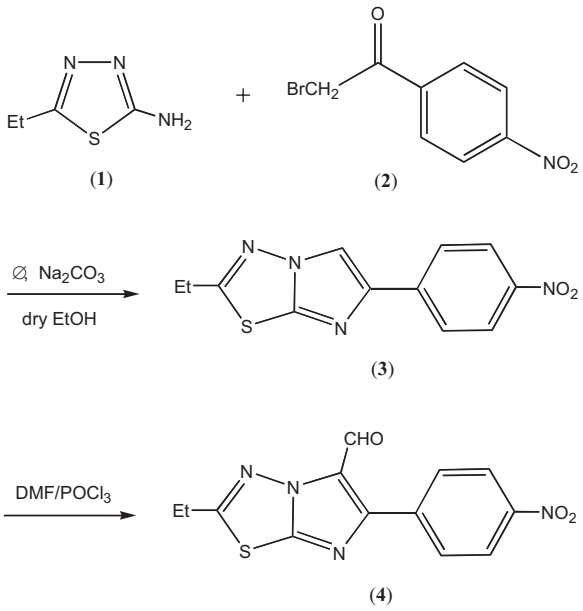
The Vilsmeier–Haack reagent was prepared by adding $POCl_3$ (3 ml) to DMF (20 ml) at 0 °C with stirring. Compound **3** (2.76 g, 0.01 mol) was added to the reagent and stirred at 0 °C for 30 minutes. The mixture was further stirred for 2 h at room temperature and at 60 °C for an additional 2 h. The reaction mixture was then poured into aqueous sodium carbonate and stirred at 90 °C for 2 h. After cooling, the mixture was diluted with water, extracted with chloroform and the chloroform extracts were washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of chloroform was recrystallised from chloroform–hexane mixture (2: 1) to get the solid aldehyde **4** as pale yellow cubic crystals (yield 70 %) m.p. 162–164 °C.

Compound **4**: IR (KBr) ; 2850 (ν_{C-H}, ald), 1674 ($\nu_{C=O}$), 1598 ($\nu_{C=N}$),1520 (ν_{NO_2}), 1473, 1445, 1370,1310 (ν_{NO_2}), 1290, 1190, 865, 710, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.49 (t, J = Hz, 3H, CH_3), 3.19 (q, J = 6 Hz, 2H, CH_2), 8.21 (d, J = 9 Hz, 2H, C_2, C_6–H, phenyl), 8.29 (d, J = 9 Hz, 2H, C_3, C_5–H, phenyl), 10.16 (s, 1H, aldehyde); ^{13}C NMR ($CDCl_3$): δ 13.5, 26.2, 124.1, 124.8, 129.9, 138.8, 148.6, 150.8, 151.5, 170.0, 177.4. Anal. Calcd for $C_{13}H_{10}N_4O_3S$; C, 51.65; H, 3.33; N, 8.53; Found C, 51.55; H, 3.28; N, 8.49 %.

X-ray analysis

Crystal data: Compound **4**: $C_{13}H_{10}N_4O_3S$, formula weight = 302.31, monoclinic, $P2_1/n$, a = 5.4725(8)Å, b = 18.531(3)Å, c = 13.3008(19)Å, β = 99.380(2)°, V = 1330.8(3)Å^3, Z = 4, μ = 0.260 mm^{-1}, D_x = 1.509 Mg/m^3, T = 293(2) K

The X-ray diffraction data were collected on a Bruker Smart CCD area detector system using MoKα (0.71073 Å) radiation for the crystal. Intensity data were collected up to a max of



Scheme 1

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

26.12° for the compound in the ω–Φ scan mode. The data were reduced using SAINTPLUS[8] and an empirical absorption correction was applied using the package SADABS.[9] A total of 11,493 reflections were collected, resulting in 3146 independent reflections of which the number of reflections satisfying $I>2\ \sigma(I)$ criteria were 2425. These were treated as observed. Corrections for Lorentz and polarisation effects were applied. The structure was solved by direct methods and difference Fourier synthesis using SHELXS97.[10] The positions of all non-hydrogen atoms were included in the full-matrix least-square refinement using SHELXL97.[11] Anisotropic refinement using full-matrix least-square procedures was carried out for a few cycles until convergence was reached. Then the hydrogen atoms were fixed geometrically and were refined isotropically. The R factor after final convergence was 0.0828 and the maximum and minimum values of residual electron density were 0.760 and –0.391 eÅ^{-3}. Molecular diagrams were generated using ORTEP[12] and the packing diagrams were generated using PLUTON[13] and CAMERON.[14] The mean plane calculation was done using the program PARST.[15]

Results and discussion

The bond distances and angles can be obtained from the CCDC. The ORTEP diagram of the molecule **4** is shown in Fig 1. Table 1 lists non-bonded and possible hydrogen-bonding interactions.

The dihedral angle 1.55° between the nitrophenyl group and the imidazo-thiadiazole ring indicate that the molecule is planar. The carbaldehyde group is coplanar with the imidazo-thiadiazole ring system and *cis* to the ethyl group.

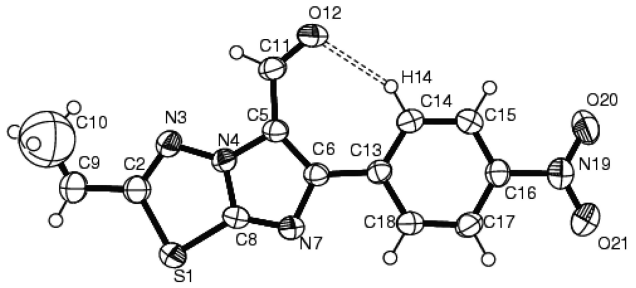


Fig. 1 The molecular structure and atom labelling scheme of the title compound (IV).

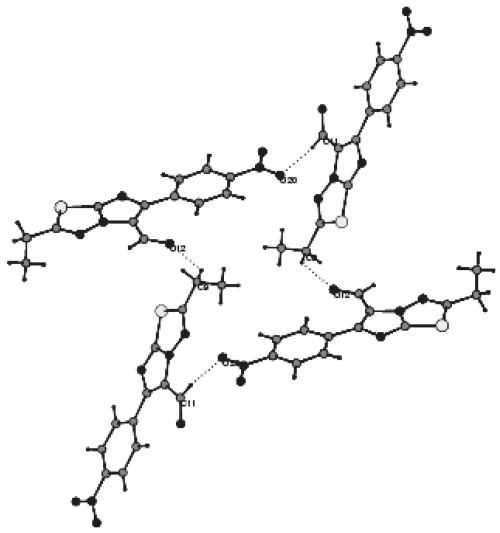


Fig. 2 Packing of the molecule: C–H···O interactions forming a tetrameric unit in the bc plane.

Table 1 Non-bonded interactions and possible hydrogen bonds (Å,°)

D–H···A	D–H	H···A	D···A	D–H···A
C14–H14···O12	0.93 (4)	2.195 (3)	3.037 (5)	150 (2)
C11–H11···O20^{i}	0.93 (4)	2.627 (3)	3.547 (5)	170 (2)
C9–H9B···O12^{ii}	0.97 (5)	2.609 (3)	3.356 (6)	134 (3)
C17–H17···N7^{iii}	0.93 (4)	2.807 (4)	3.695 (5)	158 (3)

Symmetry code (0) *x,y,z* (i) *–x*–1/2, + *y*–1/2, *–z* + 1/2 (ii) *x* + 1/2, *–y* + 1/2, + *z*–1/2 (iii) *–x* + 1, *–y* + 1, *–z*
(D–donor; A–acceptor; H–hydrogen)

The carbonyl group has a *cis* orientation with respect to the C5=C6 double bond. This leads to a strong intramolecular C14–H14···O12 hydrogen bond [C14–H14 = 0.93(4)Å, H14···O12 = 2.195{3)Å, C14···O12 = 3.037(5)Å and the angle C14–H14···O12 = 150(2)Å], leading to the formation of a conformationally locked pseudo-seven-membered ring. The nitro group is essentially planar with the adjacent aryl ring. The C–N bond distance is 1.486(8)Å. This value is typical of C(aryl) –NO_2 distances,[16] where the mean value is 1.468Å. The C–C distances in the nitrated aryl ring are between 1.310(4)Å and 1.374(5)Å. Within the nitrated aryl rings, the C–C–C angle show significant deviations from 120°. The O–N–O angle is greater than the ideal trigonal value. This can be attributed to the substantial negative charges on the paired O atoms in this unit.

The crystal structure is stabilised by intermolecular interactions of the type C–H···O and C–H···N. The former generates finite, zero dimensional tetramers (Fig. 2) in the '*bc*' plane and the latter, forms dimers along the crystallographic '*c*' axis (Fig. 3). Figure 4 shows the packing of the molecule in the unit cell. The packing motifs in accordance with Etter's

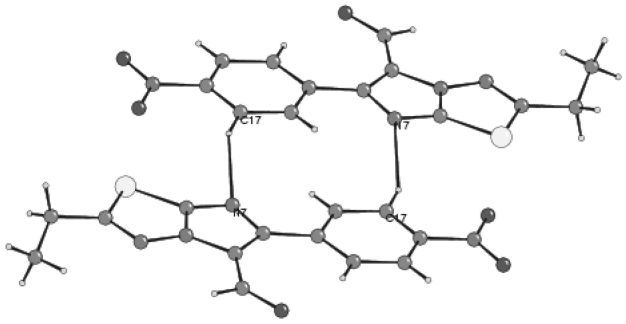


Fig. 3 C–H...N interaction via dimeric motif.

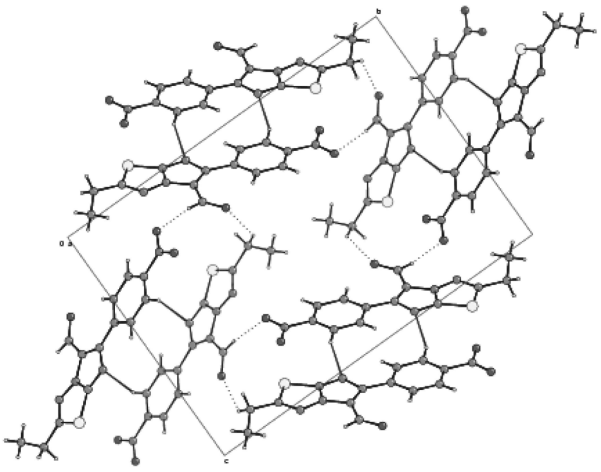


Fig. 4 Packing of the molecule showing both C–H···O and C–H···N interactions Dotted lines show C–H···O and thick lines show C–H···N interactions.

analysis are $R^4_4(36)$ corresponding to C–H···O tetramers and $R^2_2(12)$ which correspond to C–H···N intermolecular interactions. There are no aromatic π–π stacking interactions. So the supramolecular aggregation in this structure is limited to the formation of these tetrameric units and C–H···N intermolecular interactions.

Supplementary material

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The deposition number is CCDC 271065.

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References

1 M.A. Eldwy, S.A. Shams El-Din and K.M. El-Brembal, *Pharmazie*, 1979, **34**, 144.
2 A.K. Gadag, N.N. Moolvi and V.K. Rajshekar, *Bioorg. Med. Chem.,* 2004, **12**, 5651.
3 I.M. Khazi, C.S. Mahajanshetti, A.K. Gadad, A.D. Tarnalli and C. M. Sultanpur, *Arzneim.-Forsch./Drug Res.,* 1996, **46**, 949.
4 A.K. Gadad, C.S. Mahajanshetti, S. Nimbalkar and A. Raichurkar, *Eur. J. Med. Chem.,* 2000, **35**, 853
5 D.C. Thienpont, O.F.J. Vanparijs, A.H.M. Raeymaekers, J. Vandenberk, P.G.A. Demoen, F.T.N. Allewijin, R.P.H. Marsboom, C.J.E. Niemgeers, K.H.L. Shellekens and P.A.J. Janssen, *Nature*, 1966, **209**, 1084.
6 K.Y. Yamaguchi and H. Shoji, *J. Pharm. Soc. Jap*.,1954, **74**, 20.
7 G. Maffi and E. Soncin, *Bri. J. Pharmacol*., 1958, **13**, 357.
8 Bruker, SAINTPLUS. 1998, Program for data reduction. Bruker Axs Inc., Madison, Wisconsin, USA.
9 G.M. Sheldrick, SADABS (1997), Program for absorption correction. University of Göttingen, Germany.
10 G.M. Sheldrick, SHELXS97 (1997), Program for the solution of crystal structures. University of Göttingen, Germany.
11 G.M. Sheldrick, SHELXL97 (1997), Program for crystal structure refinement. University of Göttingen, Germany.
12 L.J. Farrugia, ORTEP-3 for WINDOWS – A Version of ORTEP-III with a Graphical User Interface (GUI). *J. Appl. Cryst.,* 1997, **30**, 565.
13 A.L. Spek, PLUTON (1997), Program for Molecular Graphics. University of Utrecht, The Netherlands.
14 D.M. Watkin, L. Pearce, and C.K. Prout, CAMERON (1993), Program for Molecular Graphics. Chemical Crystallography Laboratory, University of Oxford, England.
15 M. Nardelli, *Acta Cryst.,*1983, **C39**, 114.
16 F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen and R. Taylor, *J. Chem. Soc. Perkin Trans. 2,* 1987, S1.