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Synthesis, characterization and crystal structure of 2-(4-(methylthio)phenyl)-1*H*-benzo[*d*]imidazole

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ABSTRACT

An efficient synthesis of the title compound, 2-(4-(methylthio)phenyl)-1*H*-benzo[*d*]imidazole, was carried out by the condensation reaction of *o*-phenylenediamine and *p*-thiomethyl benzaldehyde in benzene. The structure was confirmed by spectroscopic data and elemental analyses. The molecular structure was determined from single crystal X-ray diffraction data. The compound crystallizes in the orthorhombic space group *Pbca* with a = 8.544(2) Å, b = 9.700(3) Å, c = 29.684(8) Å, V = 2460.0(11) Å^3, Z = 8. The crystal structure is stabilized by intermolecular C-H…N, N-H…N and π-π interactions.

1. Introduction

Benzimidazoles and their derivatives exhibit a number of important pharmacological properties, such as antihistaminic [1], anti-ulcerative [2], antiallergic [3], and antipyretic [4]. In addition, benzimidazole derivatives are effective against the human cytomegalovirus (HCMV) [5] and are also efficient selective neuropeptide Y Y1 receptor antagonists [6]. Most of the described methods for the synthesis of benzimidazoles make use of volatile organic solvents and involve solid-phase synthesis via *o*-nitroanilines [7-10] or the condensation of *o*-phenylenediamines with carboxylic acid derivatives [11], aldehydes [12-17] and aryl halides [18].

We report herein the synthesis, structure and characterization of 2-(4-(methylthio)phenyl)-1*H*-benzo[*d*] imidazole.

2. Experimental

2.1. Materials and physical measurements

All the chemicals were reagent grade; they were used as such without further purification. The solvents (methanol, ethanol, etc.) were purified according to the standard methods. The FT-IR spectra in KBr pellet was recorded on a Nicolet impact 400D spectrometer in the range 4000-400 cm^{-1}. The ^{1}H NMR spectra in $CDCl_3$ (using TMS as internal reference) was recorded on a Bruker 400 MHz spectrometer. The mass spectrum was recorded using Z-spray electrospray ionization (ESI) source on Esquire 300 plus, Bruker Daltonics. The melting point was obtained using an electrothermal melting point apparatus. Elemental analysis is carried out using elementar-Vario EI III and Carlo Erba-1108 instruments.

2.2. X-ray analysis and refinement

The X-ray diffraction data for the compound **3** was collected on a Bruker Smart CCD Area Detector System, using MoK_α (λ=0.71073 Å) radiation for the crystal. Intensity data were collected up to a maximum of 26.37° in the ω–ϕ scan mode. The data were reduced using SAINTPLUS [19]. The structure was solved by direct methods using SHELXS97 [20] and difference Fourier synthesis using SHELXL97 [20]. The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement using SHELXL97 [20] and the procedures were carried out for a few cycles until convergence was reached. A total of 17827 reflections were collected, resulting in 2520 [R_{int} = 0.0847] independent reflections of which the number of reflections satisfying I>2σ(I) criteria was 1382. These were treated as observed. The H atoms were placed at calculated positions in the riding model approximation (C-H = 0.93 Å), with their temperature factors were set to 1.2 times those of the equivalent isotropic temperature factors of the parent atoms. All other non-H atoms were refined anisotropically. The R factor for observed data finally converged to R = 0.0736 with wR_2 = 0.1351 in the compound. The maximum and minimum values of residual electron density were 0.188 and -0.156 eÅ^{-3}. Molecular diagrams were generated using ORTEP [21]. The mean plane calculation was done using the program PARST [22].

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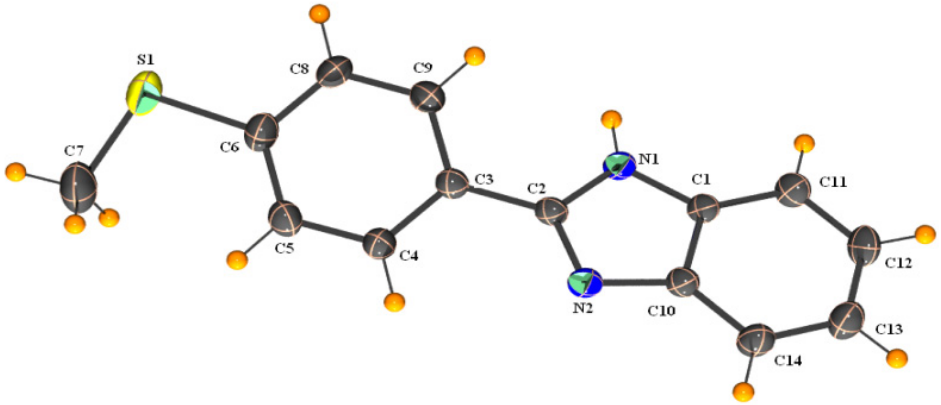
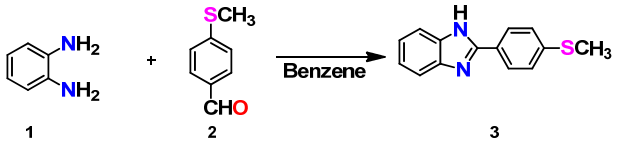


Figure 1. Molecular structure of the title compound with the atomic-numbering scheme. Displacement ellipsoids plotted at 50% probability level. Dotted line indicates intramolecular C4-H4...N2 interaction.

2.3. Synthesis

A mixture of *o*-phenylenediamine (10 mmol) and *p*-thiomethylbenzaldehyde (10 mmol) in benzene (100 mL) was refluxed for 2 h in a steam bath. On standing overnight yellow crystalline solid precipitated (Scheme 1). The yellow solid product formed was separated by filtration and washed with a mixture of water and *n*-hexane. It was recrystallised from ethanol to get pale yellow crystals and then dried in vacuum over P_2O_5. The yellow product is produced in 90% (2.34 mg) yield. M.p.: 115 °C. FT-IR (cm^{-1}): 1604 (C=N), 1471 (N-H), 1331 (C-N). ^{1}H NMR (MeOH, 400 MHz, δ ppm): 7.989 (d, *J*=10.8 MHz, 2H), 7.575 (m, 2H), 7.378 (d, *J*=8.8 MHz, 4H), 7.224 (m, 2H), 4.82 (s, 1H), 2.533 (s, 3H). ESI-MS (m/z): 240 (M^++1). Anal. Calcd. for $C_{14}H_{12}N_2S$.: C, 70.01; H, 5.04; N, 11.66; S, 13.32. Found: C, 69.71; H, 4.32; N, 12.41; S, 12.95.



Scheme 1

3. Results and discussion

The various bands seen in the IR spectrum of compound **3** have been assigned to the bending modes of vibration of different groups present in the organic compound. The band at 3441 cm^{-1} due to the stretching vibration of NH_2 in *o*-phenylenediamine is not observed in the IR spectrum of compound **3**. This implies the formation of compound **3** formation of compound **3** via a condensation reaction between *o*-phenylenediamine and *p*-methoxybenzaldehyde. A strong C=N stretching band in the IR spectrum of compound **3** seems to occur at around 1604 cm^{-1}. In the ^{1}H NMR spectrum the singlet for the thiomethyl protons appeared at δ 2.53 ppm and the characteristic broad singlet for the proton of N_1 appeared at δ 4.82 ppm. The signals for the aromatic protons were also noted in Section 2.3.

Figure 1 shows the ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability of the title compound. Table 1 gives the crystal data and the structure refinement. Selected bond lengths and bond angles are presented in Table 2. All non-bonded interactions are tabulated in Table 3. The benzimidazole and thiomethyl phenyl groups are non-planar with a dihedral angle of 26.73(2)° between them. The thiomethyl group is *cis* to benzimidazole ring. The molecular structure is primarily stabilized by a weak intramolecular C4-H4...N2 hydrogen bond [C4-H4 = 0.930 Å, H4...N2 = 2.702(3) Å, C4...N2 = 2.969(5) Å and the angle C4-H4...N2 = 97.41(3)°] leading to the formation of a pseudo-five-membered hydrogen-bonded pattern (S(5) according to Etter's graph set analysis [23,24]). This pseudo-five-membered ring locks the molecular conformation and eliminates conformational flexibility. The bond lengths and angles for the benzimidazole moiety of the molecule are in good agreement, within experimental errors, with those observed in other benzimidazole derivatives [25-31]. The N1-C2 and N2-C2 distances were found to be 1.356(4) Å and 1.325(4) Å, respectively. The *cis* orientation of the thiomethyl group and phenyl ring is characterized by the torsion angle C5-C6-S1-C7 = 16.6(4)° in the molecule. Additionally, the crystal structure is stabilized by intermolecular [C-H...N and N-H...N] bonds. The C4-H4...N1 and N1-H1...N2 interactions together generates bifurcated hydrogen bonds from two donors, C4 and N2, to the same acceptor, N1. These bifurcated hydrogen bonds link the dimers into zig-zag tapes along the crystallographic '*a*' axis (Figure 2). Additionally, the supramolecular assembly is further stabilized by π-π stacking interactions between the benzimidazole and thiomethyl phenyl rings (Figure 3). The C8...C14 (-1+*x*, *y*, *z*) disposed at a distance of 3.742(5) Å.

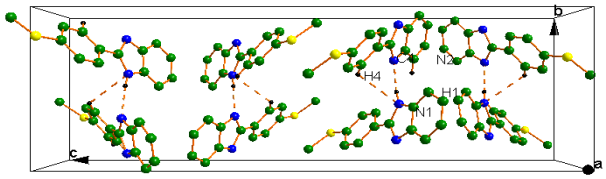


Figure 2. Packing diagram of **3** viewed along the '*a*' axis. Dotted lines indicates C4-H4...N1 and N1-H1...N2 intermolecular interactions.

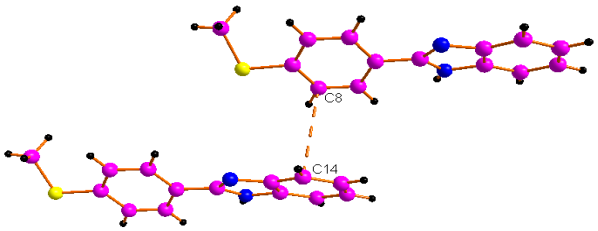


Figure 3. View of the molecular packing in **3**, showing π-π stacking interactions between the benzimidazole and thiomethyl phenyl rings.

Table 1. Crystal data and structure refinement for compound **3**.

Empirical formula	$C_{14}H_{12}N_2S$
Formula weight	240.32
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 8.544(2)Å
	b = 9.700(3) Å
	c = 29.684(8) Å
Volume	2460.0(11) Å^3
Z	8
Calculated density	1.298 Mg/m^3
Absorption coefficient	0.241 mm^{-1}
F(000)	1008
Crystal size	0.40 x 0.35 x 0.30 mm
Theta range for data collection	1.37 to 26.37°
Limiting indices	$-10 \le h \le 10$
	$-12 \le k \le 11$
	$-36 \le l \le 37$
Reflections collected / unique	17827/2520 [R(int) = 0.1166]
Completeness to theta	26.37 100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2520 / 0 / 155
Goodness-of-fit on F^2	0.962
Final R indices [I>2sigma(I)]	R1 = 0.0736, wR2 = 0.1351
R indices (all data)	R1 = 0.1496, wR2 = 0.1676
Largest diff. peak and hole	0.188 and -0.156 e. Å^{-3}
Measurement	Bruker SMART CCD diffractometer
Program system	SAINTPLUS
Structure determination	Direct methods (SHELXL97, SHELXS97)
Molecular graphics	ORTEP-3 (Farrugia, 1997)
CCDC	763065

Table 2. Selected geometric parameters (Å, °) for 2-(4-(methylthio)phenyl)-1*H*-benzo[*d*]imidazole.

Bond lengths			
C1-N1	1.373(4)	C6-C8	1.393(5)
C1-C11	1.384(5)	C6-S1	1.764(4)
C1-C10	1.394(5)	C7-S1	1.771(5)
C2-N2	1.325(4)	C8-C9	1.370(5)
C2-N1	1.356(4)	C10-C14	1.390(5)
C2-C3	1.463(5)	C10-N2	1.397(4)
C3-C4	1.384(5)	C11-C12	1.379(5)
C3-C9	1.394(5)	C12-C13	1.389(5)
C4-C5	1.382(5)	C13-C14	1.370(5)
C5-C6	1.385(5)		
Bond Angles			
N1-C1-C11	132.0(3)	C8-C6-S1	117.1(3)
N1-C1-C10	105.6(3)	C9-C8-C6	120.7(4)
C11-C1-C10	122.4(3)	C8-C9-C3	121.1(4)
N2-C2-N1	112.4(3)	C14-C10-C1	120.1(3)
N2-C2-C3	124.5(3)	C14-C10-N2	130.4(3)
N1-C2-C3	123.1(3)	C1-C10-N2	109.5(3)
C4-C3-C9	118.0(3)	C12-C11-C1	116.6(3)
C4-C3-C2	120.7(3)	C11-C12-C13	121.5(3)
C9-C3-C2	121.3(3)	C14-C13-C12	121.8(4)
C5-C4-C3	121.3(3)	C13-C14-C10	117.6(3)
C4-C5-C6	120.4(4)	C2-N1-C1	107.6(3)
C5-C6-C8	118.6(3)	C2-N2-C10	104.9(3)
C5-C6-S1	124.3(3)	C6-S1-C7	103.1(2)

Table 3. Non-bonded interactions and possible hydrogen bonds (Å, °) for compound **3** (D-donor; A-acceptor; H-hydrogen).

D—H···A	D—H	H···A	D···A	D—H···A
C4-H4...N2	0.930(4)	2.702(3)	2.969(5)	98
C4-H4...N1	0.930(4)	2.948(3)	3.446(4)	115
N1-H1...N2	0.860(3)	2.023(3)	2.856(4)	162

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Supplementary material

CCDC-763065 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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