Synthesis, spectroscopic and crystal structure analysis of 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile and -3-carboxamide

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The preparation of 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide via the intermediate 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile is described, along with details of the crystal structure analysis of both compounds.

Keywords: 1-benzothiophenes, *o*-aminonitriles, dimedone, crystal structures

Benzothiophenes are heterocycles which are important both as biologically active molecules as well as luminescent components in certain organic materials.[1-3] One of the well-known FDA approved drugs containing the benzothiophene system is Raloxifene, used to treat osteoporosis in postmenopausal women.[4-6] Raloxifene is also being researched actively for its other potential applications, one of them being its pharmaceutical action against Alzheimer's disease.[7] In the same series, a number of 3-(4-pyridinyl)aminobenzothiophenes are under investigation for use in the treatment of diseases involving the central nervous system such as obsessive–compulsive disorders.[8-9]

The versatile use of 2-amino-3-cyanothiophenes in the syntheses of numerous polyfused heterocycles such as thienopyrimidines, thienotriazolopyrimidines and pyridothienopyrimidines is well documented in the literature. Additionally, benzothiophenes are important components in liquid crystal research.[10]

The variety of pharmaceutical functions shown by benzothiophene derivatives prompted us to carry out structural analyses of these compounds, with the intention to gain a better understanding of the nature of their structure–activity correlations. As a part of our own research in this area, we present here the syntheses and structure determination of the two related tetrahydrobenzothiophenes, 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (**2**) and the corresponding 3-carboxamide (**3**).

Results and discussion

The amino-amide **3** was synthesised by the acid hydrolysis of 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (**2**), which in turn was prepared by the reaction of dimedone (**1**), malononitrile and sulfur under conditions reported by Gewald.[11] (Scheme 1)

IR and ^{1}H NMR spectroscopic analysis confirmed the presence of the NH_2 group and the other structural elements of the molecules.

The crystal structure analyses were carried out for both **2** and **3** by single crystal X-ray diffraction. The thiophene moieties are planar in both compounds, and the cyclohexene ring in both assumes an envelope conformation. In **3**, an intramolecular N–H···O bond helps to establish the molecular conformation. The molecular packing of **2** as well as of **3** is augmented by intermolecular N-H···O bonds.

Figure 1 shows the ORTEP plot of the compound **2**, and Fig. 2 shows its hydrogen bond interactions and crystal packing. Figure 3 shows the ORTEP plot of compound **3**, and Fig. 4 shows the hydrogen bond interactions and crystal packing of that compound. The selected bond distances and angles are given in Tables 1 and Table 2 for compounds **2** and **3** respectively. Tables 3 and 4 show the respective hydrogen bond interactions for compounds **2** and **3.**

2-Amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (**2**): In the molecule of **2** (Fig.1), the thiophene ring is planar while the cyclohexene ring is in an envelope conformation, as indicated by its ring analysis data.[12] This is rather unusual since literature survey reveals that in most of the benzothiophene ring systems the cyclohexyl ring adopts a half-chair conformation.[13-15]

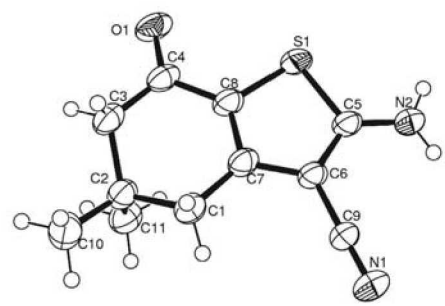
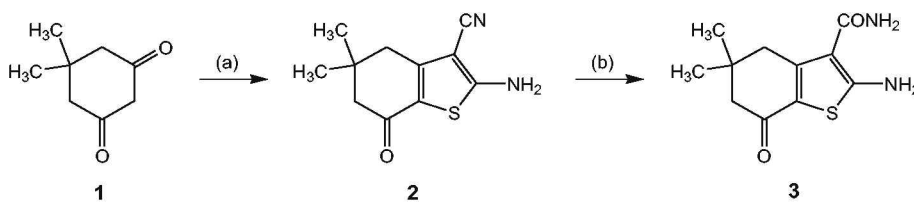


Fig. 1 The molecular structure and atom labelling scheme of compound **2.**



Scheme 1 Reagents: (a) i: $CH_2(CN)_2$, Et_3N, Δ; ii: S_8, Et_2NH, Δ; (b): c. H_2SO_4, 0 °C; NH_4OH

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Table 1 Selected bond lengths [Å] and angles [°] for compound **2**

Bond	Length (Å)	Bonds	Angle (°)
C1–C7	1.494(3)	C10–C2–C11	109.55(17)
C2–C10	1.522(3)	C3–C4–C8	115.55(15)
C2–C11	1.522(3)	C3–C4–O1	122.67(17)
C3–C4	1.497(3)	C8–C4–O1	121.78(18)
C4–C8	1.437(2)	C6–C5–S1	110.91(13)
C4–O1	1.232(2)	C6–C5–N2	128.01(16)
C5–C6	1.399(2)	S1–C5–N2	121.06(14)
C5–S1	1.730(2)	C5–C6–C7	113.45(14)
C5–N2	1.326(3)	C5–C6–C9	122.13(16)
C6–C7	1.412(2)	C7–C6–C9	124.42(16)
C6–C9	1.425(2)	C1–C7–C6	126.83(15)
C7–C8	1.370(2)	C1–C7–C8	121.34(16)
C8–S1	1.741(2)	C6–C7–C8	111.83(16)
C9–N1	1.139(2)	C4–C8–C7	124.35(18)
		C4–C8–S1	122.94(14)
		C7–C8–S1	112.69(14)
		C6–C9–N1	178.9(2)
		C5–S1–C8	91.12(8)

The crystal packing consists of N–H···O hydrogen bonds (Fig. 2). The supramolecular cohesion is further strengthened by π–π stacking interactions between benzothiophene rings with C4–C5 atoms of two molecules being separated by a distance of 3.981(2)Å (symmetry code: 1–*x*, ½ + *y*, ½ + *z*).

2-Amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (**3**): In the molecule of **3** (Fig. 3), the cyclohexene and thiophene rings are coplanar. An intramolecular N–H···O bond forms a pseudo-six-membered ring with graph set $S^1_1(6)$, thus locking the molecular conformation and eliminating conformational

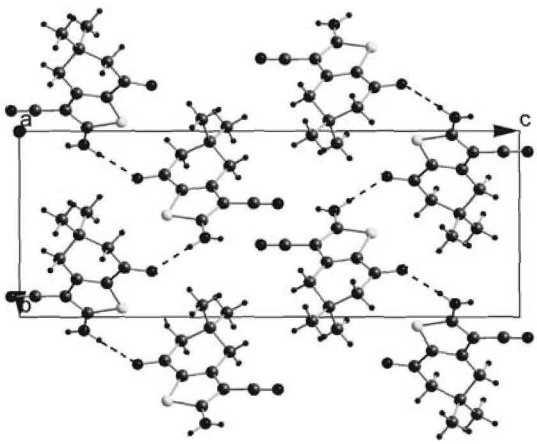

Fig. 2 Packing of the molecules of **2** with N-H···O hydrogen bond interactions, viewed down the *a* axis.

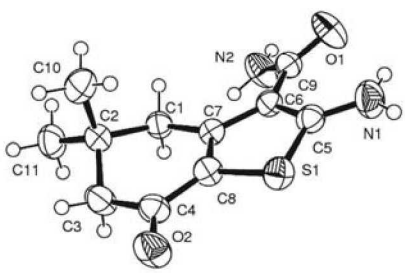

Fig. 3 The molecular structure and atom labelling scheme of compound **3**.

Table 2 Selected bond lengths [Å] and angles [°] for compound **3**

Bond	Length (Å)	Bonds	Angle (°)
C1–C7	1.507(4)	C3–C2–C10	110.5(3)
C2–C3	1.533(4)	C2–C3–C4	115.1(2)
C2–C10	1.534(5)	C3–C4–C8	115.7(3)
C3–C4	1.506(4)	C3–C4–O2	121.2(3)
C4–C8	1.430(4)	C8–C4–O2	123.1(3)
C4–O2	1.238(3)	C6–C5–N1	127.7(3)
C5–C6	1.400(4)	C6–C5–S1	112.3(3)
C5–N1	1.337(4)	N1–C5–S1	120.0(2)
C5–S1	1.734(3)	C5–C6–C7	111.6(2)
C6–C7	1.426(4)	C5–C6–C9	120.1(2)
C6–C9	1.476(4)	C7–C6–C9	128.2(3)
C7–C8	1.377(4)	C1–C7–C6	128.0(2)
C8–S1	1.741(2)	C1–C7–C8	119.2(2)
C9–N1	1.139(2)	C6–C7–C8	112.8(2
		C4–C8–C7	125.2(3)
		C4–C8–S1	122.4(2)
		C7–C8–S1	112.4(2)
		C6–C9–N2	118.1(3)
		C6–C9–O1	121.2(3)
		N2–C9–O1	120.6(3)
		C5–S1–C8	90.83(14)

flexibility. Here again the cyclohexene ring is in an envelope conformation and ring analysis data[12] is indicative of this.

In the crystal structure of **3**, the molecules are interconnected via two types of N–H···O bond. One of them involves N2–H2A···O1 forming a zig-zag pattern along the crystallo-

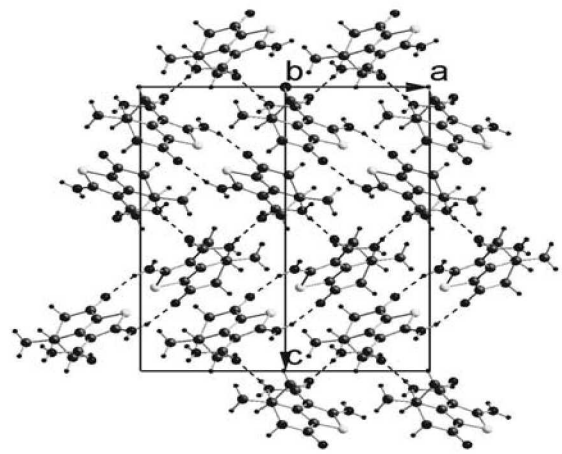

Fig. 4 Packing of the molecules in the crystal of 3, showing intermolecular hydrogen bonds.

Table 3 Non-bonded interactions and possible hydrogen bonds (Å,°) for compound **2** (D – donor; A – acceptor; H – hydrogen)

D–H···A	D–H	H···A	D···A	Angle D–H···A
N2–H1N···O1	0.839(3)	2.050(3)	2.862(2)	162.8(1)

Symmetry code: –*x*, –1/2 + *y*, ½–*z*.

Table 4 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	Angle D–H···A
N1–H1D···O2^{i}	0.860(2)	2.017(2)	2.836(4)	158.8(2)
N2–H2A···O1^{ii}	0.860(3)	2.064(3)	2.902(4)	164.4(2)
N1–H1C···O1	0.860(2)	2.203(3)	2.780(4)	124.2(2) intra

Symmetry codes: (i) –*x* + 1, + *y*–1/2,–*z* + 1/2 (ii) *x*–1/2,–*y*–1/2,–*z*.

graphic *c* axis and the other consists of N1–H1D···O2 bonds generating helices along the same *c* axis, thus giving rise to a three-dimensional network structure. The molecular packing is shown in Fig. 4.

Experimental

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

Synthesis and characterisation

2-Amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (**2**): A mixture of dimedone (**1**) (1.4 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and triethylamine in dry ethanol (10%w/v, 10 mL) was refluxed for 6 h. Solvent and generated water were removed under reduced pressure. To the residue was added dry ethanol (10 mL), elemental sulfur (0.336 g, 10.5 mgatom) and diethylamine (1 mL) and the reaction mixture was refluxed for 8 h. A yellow solid which separated was filtered off, washed with ethanol, dried, and recrystallised from ethanol–dioxan to afford bright yellow needles of the amino-nitrile **2**[16] (1.7 g, 76%) m.p. 242–244 °C. IR: ν_{max} 3339, 3190, 2962, 2901, 2213, 1645, 1623 cm^{-1}. NMR (DMSO-d_6): δ_H 0.99 (s, 6H,, Me_2), 2.27 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 8.30 (s, 2H, NH_2, D_2O exchangeable). Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: 59.79; H, 5.55; N, 12.81%.

2-Amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (**3**): To concentrated sulfuric acid (55 mL) stirred at 0 °C was added 2-amino-benzothiophene-3-carbonitrile (15 g, 0.068 mol) in portions over 10 minutes. The cold bath was removed and the reaction mixture was stirred at ambient temperature for 5 h. The reaction was poured cautiously onto crushed ice and stirred for 1 h. The cooled solution was neutralised by addition of concentrated ammonium hydroxide in portions. The resultant precipitate was collected, washed from water and recrystallised from alcohol to afford yellow flakes (9.7 g, 60%), m.p. 250–252 °C. IR: ν_{max} 3483, 3392, 3333, 3269, 2954, 2928, 1637, 1596 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H 1.05 (s, 6H, Me_2), 2.28 (s, 2H, CH_2), 2.53 (s, 2H, CH_2), 6.9 (s, 2H, NH_2, D_2O exchangeable), 7.9 (s, 2H, $CONH_2$, D_2O exchangeable). Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.46; H, 5.86; N, 11.76. Found: 55.43; H, 5.72; N, 11.81%.

Crystals suitable for diffraction were obtained by slow evaporation from a solution in chloroform.

Crystal structure determination

The X-ray diffraction data for both compounds were collected on a Bruker Smart CCD Area Detector System using Mo–Kα (0.71073Å) radiation. Intensity data were collected up to a maximum of 27.82° and 28.26° for the compounds **2** and **3** respectively in the ω–ϕ scan mode. The data were processed using SAINTPLUS.[17] The structures were solved by direct methods using SHELEXS[18] and difference Fourier synthesis using SHELXL97.[19] The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the refinements by full matrix least-squares methods using SHELXL97.[19] Molecular diagrams were generated using ORTEP.[20]

For compound **2**, a total of 9347 reflections was collected, resulting in 2561 (R_{int} = 0.0287) independent reflections of which the number of reflections satisfying $I > 2\ \sigma(I)$ criterion was 1956. These were treated as observed. For compound **3**, this order was 7742/2933 (R_{int} = 0.0413)/2344. The hydrogen atoms were fixed geometrically and were refined isotropically for both structures. The R factor and wR_2 for all data were 0.061 and 0.106 respectively for compound **2** while for compound **3** these values were 0.066 and 0.129. The R factor for observed data finally converged to 0.0422 with wR_2 = 0.0969 in the case of compound **2** and for compound **3**, R = 0.0461 with wR_2 = 0.1007. The maximum and minimum values of residual electron density were 0.264 and –0.193 eÅ^{-3} for compound **2.** In the case of compound **3**, these values were 0.279 and –0.280eÅ^{-3}.

Crystal data (**2**): $C_{11}H_{12}N_2OS$, formula weight = 220.29, monoclinic, $P2_1/c$, a = 5.7812(4)Å, b = 8.5433(6)Å, c = 22..6148(16) Å, β = 96.6200(10)°, V = 1109.51(13)Å^3, Z = 4, μ = 0.266 mm^{-1}, D_x = 1.319 Mg m^{-3}, T = 293(2)K.

Crystal data (**3**): $C_{11}H_{14}N_2O_2S$, formula weight = 238.30, orthorhombic, $P2_12_12_1$, a = 7.252(3)Å, b = 9.349(4)Å, c = 17.542(8)Å, V = 1189.3(9)Å^3, Z = 4, μ = 0.259 mm^{-1}, D_x = 1.331 Mg/m^3, T = 293(2)K.

Supplementary material

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge data centre. The deposition numbers are CCDC 686217 (compound **2**) and CCDC 686218 (compound **3**).

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