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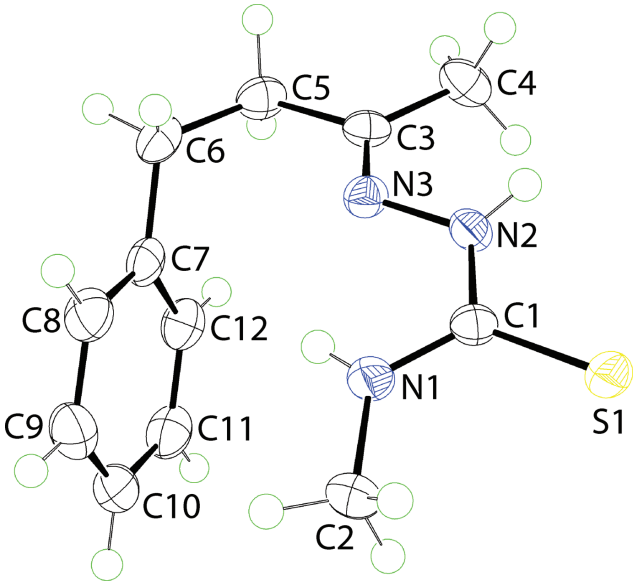
Crystal structure of 3-methyl-1-[(*E*)-(4-phenylbutan-2-ylidene)amino]thiourea, $C_{12}H_{17}N_3S$



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Abstract

$C_{12}H_{17}N_3S$, monoclinic, $P2_1/c$ (no. 14), $a = 9.3084(19)$ Å, $b = 7.9523(16)$ Å, $c = 16.905(3)$ Å, $\beta = 92.26(3)°$, $V = 1250.4(4)$ Å^3, $Z = 4$, $R_{gt}(F) = 0.0330$, $wR_{ref}(F^2) = 0.0914$, $T = 100(2)$ K.

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The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colourless prism
Size:	0.24 × 0.10 × 0.06 mm
Wavelength:	Cu $K\alpha$ radiation (1.5418 Å)
μ:	2.11 mm^{-1}
Diffractometer, scan mode:	Oxford Diffraction Gemini, ω
θ_{max}, completeness:	71.3°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	13212, 2413, 0.024
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 2215
$N(param)_{refined}$:	153
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3], WinGX/ORTEP [4]

Source of material

4-Methyl-3-thiosemicarbazide (Alfa Aesar), 4-phenylbutanone (Acros Organic), absolute ethanol (Merck), acetonitrile (Merck) and ethyl acetate (Merck) were of analytical grade and used as purchased. 4-Methyl-3-thiosemicabazide (1.0516 g, 0.01 mol) was dissolved in hot absolute ethanol (20 mL) and then 4-phenylbutanone (1.50 mL, 0.01 mol) was added slowly while stirring and heating (348 K) for about 20 min. The white precipitate was filtered, washed with cold ethanol and dried in vacuo then dissolved in a mixture of acetonitrile and ethyl acetate (2:1 v/v). Single crystals were grown at room temperature by the slow evaporation of the solution. Yield: 89%. **M. Pt** 368–369 K. **FT-IR** (ATR (solid) cm^{-1}): 3133 ν(Ar C–H), 3317 ν(N–H), 3000 ν(=C–H), 2754 ν(C–H), 1602 ν(C=N), 1239 ν(N–N), 1058 ν(C=S). **^{1}H-NMR** (500 MHz, $CDCl_3$, ppm): δ 8.45 (s, 1H, S=CN(H)N), 7.35 (s, 1H, S=CN(H)N), 7.27–7.30 (m, 2H, H9, H11), 7.21 (d, 1H, $J = 7.3$ Hz, H10), 7.18 (d, 2H, $J = 7.6$ Hz, H8, H12), 3.17 (d, 3H, $J = 4.7$ Hz, H2), 2.87 (t, 2H, $J = 7.7$ Hz, H6), 2.60 (t, 2H, $J = 7.7$ Hz, H5), 1.87 (s, 3H, H4). **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$, ppm): δ 178.9 (C1), 151.0 (C3), 140.9 (C7), 128.6 (C8, C12), 128.2 (C9, C11), 126.2 (C10), 40.0

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
S1	0.71062(3)	0.93907(4)	0.45494(2)	0.01953(13)
N1	0.79356(12)	0.74224(15)	0.57708(7)	0.0207(3)
H1N	0.7656(18)	0.6735(18)	0.6128(8)	0.025*
N2	0.55323(12)	0.74931(14)	0.54609(7)	0.0185(2)
H2N	0.4810(13)	0.8089(18)	0.5283(9)	0.022*
N3	0.54024(12)	0.64202(14)	0.61034(6)	0.0185(2)
C1	0.68733(14)	0.80478(16)	0.53119(8)	0.0170(3)
C2	0.94563(14)	0.7699(2)	0.56540(9)	0.0262(3)
H2A	0.974316	0.708782	0.518231	0.039*
H2B	1.001822	0.729295	0.611779	0.039*
H2C	0.963258	0.890389	0.558321	0.039*
C3	0.42008(14)	0.56576(16)	0.61675(8)	0.0185(3)
C4	0.29254(14)	0.58452(18)	0.56022(9)	0.0246(3)
H4A	0.249036	0.695496	0.567167	0.037*
H4B	0.221728	0.497014	0.570858	0.037*
H4C	0.323643	0.573290	0.505761	0.037*
C5	0.40771(15)	0.44824(18)	0.68564(9)	0.0226(3)
H5A	0.393302	0.332837	0.664835	0.027*
H5B	0.320696	0.478875	0.714244	0.027*
C6	0.53605(16)	0.44630(18)	0.74498(8)	0.0228(3)
H6A	0.548857	0.561366	0.766472	0.027*
H6B	0.511901	0.372266	0.789624	0.027*
C7	0.67865(15)	0.38873(17)	0.71409(8)	0.0206(3)
C8	0.80552(16)	0.46118(19)	0.74471(8)	0.0257(3)
H8	0.800468	0.545411	0.784353	0.031*
C9	0.93906(17)	0.4131(2)	0.71859(9)	0.0294(3)
H9	1.023973	0.464014	0.740454	0.035*
C10	0.94842(16)	0.2906(2)	0.66059(9)	0.0276(3)
H10	1.039316	0.257960	0.642048	0.033*
C11	0.82313(17)	0.21648(19)	0.62999(9)	0.0271(3)
H11	0.828584	0.131930	0.590523	0.032*
C12	0.68985(16)	0.26466(17)	0.65652(8)	0.0234(3)
H12	0.605243	0.212271	0.635093	0.028*

(C5), 32.4 (C2), 31.1 (C6), 16.0 (C4). **GC-MS(EI)**: m/z calcd. for $C_{12}H_{17}N_3S^+ = [M^+] = 235$, found 235.

Experimental details

The C-bound H atoms were geometrically placed (C—H = 0.95–0.98 Å) and refined as riding with $U_{iso}(H) = 1.2–1.5U_{eq}(C)$. The N-bound H atoms were refined with N—H = 0.88 ± 0.01 Å, and with $U_{iso}(H) = 1.2U_{eq}(N)$.

Comment

Thiosemicarbazone derivatives, i.e. molecules with general formula RN(H)C(=S)N(H)N=CR′, have been known for well over a century [5]. The 1,2-di-substituted thiourea derivatives can be readily prepared from the reaction of thiosemicarbazide, $H_2NC(=S)NHNH_2$, with an aldehyde or ketone. Two thiosemicarbazone drugs, Methisazone and Thioacetazone, are among those which have been used in the past. Methisazone, an anti-viral drug, is produced by the condensation of *N*-methylisatin with thiosemicarbazide and has recently been studied for repurposing for the treatment of COVID-19 [6]. Although the use of thioacetazone, $H_2NC(=S)N(H)N=CC_6H_4$-4-$N(H)C(=O)CH_3$, is no longer recommended, there has been interest in some of its derivatives [7] to be employed against Mycobacterium tuberculosis. Metal complexes of thiosemicarbazones are also known to possess biological activity [8] and that is a key motivation for on-going studies in this area [9, 10]. With this in mind, the synthesis of a thiosemicarbazone derivative was attempted and herein, the crystal and molecular structures of $MeN(H)C(=S)N(H)N=C(H)CH_2CH_2Ph$, (I), are described.

The molecular structure of (I) is shown in the figure (70% displacement ellipsoids) and adopts a distinctive, U-shape conformation. This is evidenced in the sequence of C1—N2—N3—C3 [−167.97(12)°], N2—N3—C3—C5 [179.13(11)°], N3—C3—C5—C6 [5.73(18)°] and C3—C5—C6—C7 [−62.76(16) Å] torsion angles with a dramatic twist about the C3—C5 bond. The stabilisation of this arrangement comes about, at least in part, due to the formation of an intramolecular amine-N—H···π(phenyl) [N1—H1n···Cg(C6—C11): = H1n···Cg(C6—C11) = 2.970(14) Å with angle at H1n = 145.1(13)°] interaction. It is also noted that this same N—H atom participates in an intramolecular hydrogen bond with the imine-N atom [N1—H1n···N3: H1n···N3 = 2.111(17) Å, N1—N3 = 2.5722(17) Å with angle at H1n = 112.9(13)°] indicating this atom may be considered bifurcated. The C1, N1, N2 and S1 atoms comprising the chromophore are strictly planar, exhibiting a r.m.s. deviation of 0.0086 Å, with the appended N3 and C2 atoms lying 0.0393(18) and 0.143(3) Å to either side of this plane. The conformation about the imine C3 = N3 [1.2807(18) Å] is *E*, and the thioamide-N—H and -S atoms are *syn*.

In the only other crystallographically characterised thiosemicarbazone structure with an ethylene link between the imine and phenyl residues, i.e. differing only from (I) by having a methoxy group in the 4-position of the phenyl ring [11], the molecule is flat in the $-CH_2CH_2-$ region (all-*trans*) and is approximately co-planar with the C=NN(H)C(=S)N(H)Me residue. It is also of interest to compare the structure of (I) with that of the unsaturated derivative, i.e. with a C5 = C6 double-bond [12]. By contrast to (I), this adopts, to a first approximation, a planar structure.

The key feature of the molecular packing in the crystal of (I) is the formation of centrosymmetric dimers *via* amide-N—H···S(thione) hydrogen bonds [N2—H2n···S1^i: H2n···S1^i = 2.705(13) Å, N2···S1^i = 3.4885(14) Å with angle at H2n = 151.0(13)° for symmetry operation (i) $1-x$, $2-y$, $1-z$] leading to an eight-membered $\{\cdots HNCS\}_2$ synthon, which has a flattened chair conformation. The only

other directional interactions noted in the crystal are of the type methylene-C—H···N(imine) [C6—H6b···N3^{ii}: H6b···N3^{ii} = 2.55 Å, C6···N3^{ii} = 3.5325(19) Å with angle at H6b = 171° for (ii) $1-x$, $-1/2+y$, $3/2-z$]. These connect the dimeric aggregates into a supramolecular layer in the *bc*-plane; the planes stack without directional interactions between them. This observation prompted a further investigation of the molecular packing by the calculation of the Hirshfeld surfaces and the full and delineated two-dimensional fingerprint plots with the use of Crystal Explorer 17 [13] and established procedures [14].

Despite the fingerprint plot delineated into H···S/S···H contacts showing characteristic sharp spikes ascribed to the N—H···S hydrogen bonds, the total contribution to the calculated Hirshfeld surface is 16.3%, i.e. considerably less than contributed by H···H contacts, at 62.2%. The only other two significant contributions to the surface are from H···C/C···H [14.0%] and H···N/N···H [7.3%] contacts.

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