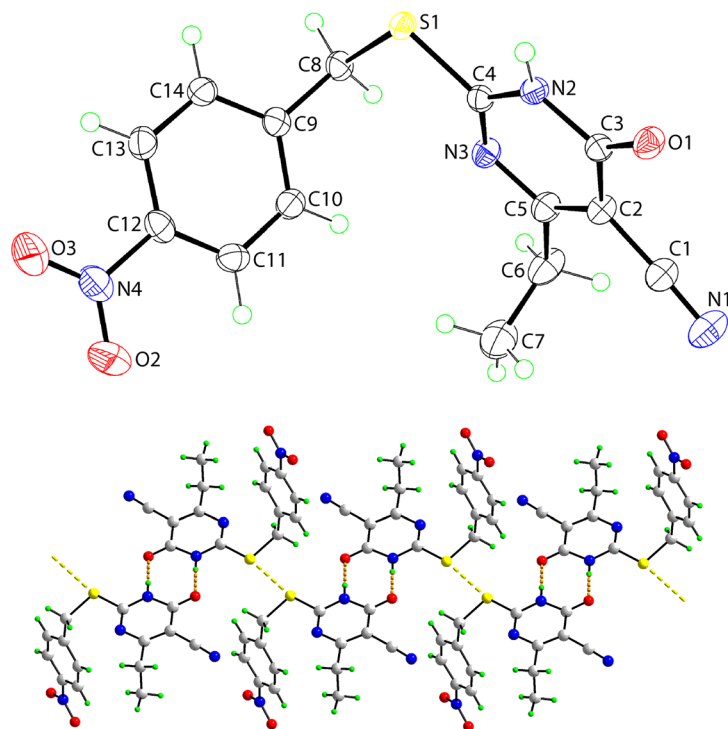


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Crystal structure of 4-ethyl-2-[[4-nitrophenyl]methyl]sulfanyl]-6-oxo-1,6-dihydropyrimidine-5-carbonitrile, $C_{14}H_{12}N_4O_3S$



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Abstract

$C_{14}H_{12}N_4O_3S$, monoclinic, $P2_1/n$ (no. 14), $a = 12.2777(3)$ Å, $b = 9.4312(2)$ Å, $c = 12.9412(2)$ Å, $\beta = 107.945(2)^\circ$, $V = 1425.61(5)$ Å³, $Z = 4$, $R_{gt}(F) = 0.0305$, $wR_{ref}(F^2) = 0.0837$, $T = 160$ K.

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Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.27 × 0.22 × 0.10 mm
Wavelength:	Cu $K\alpha$ radiation (1.54184 Å)
μ :	2.20 mm ⁻¹
Diffractometer, scan mode:	XtaLAB Synergy, ω
θ_{max} , completeness:	74.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int} :	14,965, 2903, 0.015
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2 \sigma(I_{obs})$, 2866
$N(param)_{refined}$:	203
Programs:	CrysAlis ^{PRO} [1], SHELX [2, 3], WinGX/ORTEP [4]

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.

Source of material

To a solution of the 6-ethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile [5] (1.81 g, 0.01 mol)

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	x	y	z	U_{iso}^*/U_{eq}
S1	0.90018 (2)	0.88851 (3)	0.44589 (3)	0.02485 (11)
O1	0.88985 (7)	0.37185 (9)	0.43821 (7)	0.0259 (2)
O2	0.58994 (12)	1.00783 (15)	0.82809 (10)	0.0571 (4)
O3	0.73808 (13)	1.14015 (17)	0.89395 (10)	0.0612 (4)
N1	0.59363 (10)	0.25275 (13)	0.32561 (11)	0.0383 (3)
N2	0.88179 (9)	0.61296 (10)	0.42934 (8)	0.0211 (2)
H2N	0.9557 (8)	0.6164 (16)	0.4686 (11)	0.025*
N3	0.70988 (9)	0.73915 (11)	0.35590 (8)	0.0242 (2)
N4	0.67383 (11)	1.07119 (14)	0.82016 (10)	0.0353 (3)
C1	0.64715 (11)	0.35453 (14)	0.33928 (11)	0.0277 (3)
C2	0.70985 (10)	0.48497 (13)	0.35747 (10)	0.0236 (3)
C3	0.83199 (10)	0.48011 (12)	0.41035 (9)	0.0212 (2)
C4	0.82020 (10)	0.73396 (12)	0.40587 (9)	0.0208 (2)
C5	0.65455 (11)	0.61319 (13)	0.33133 (10)	0.0251 (3)
C6	0.52736 (12)	0.62386 (15)	0.27902 (13)	0.0369 (3)
H6A	0.500585	0.543255	0.228556	0.044*
H6B	0.509062	0.712690	0.236411	0.044*
C7	0.46546 (13)	0.62242 (18)	0.36451 (17)	0.0499 (5)
H7A	0.383469	0.638330	0.329430	0.075*
H7B	0.496242	0.697665	0.417729	0.075*
H7C	0.476845	0.530330	0.401382	0.075*
C8	0.78959 (11)	1.02412 (13)	0.42600 (10)	0.0247 (3)
H8A	0.819023	1.115372	0.407696	0.030*
H8B	0.722190	0.996837	0.364393	0.030*
C9	0.75399 (10)	1.04231 (12)	0.52650 (10)	0.0229 (2)
C10	0.66152 (11)	0.96726 (14)	0.53959 (10)	0.0268 (3)
H10	0.617580	0.908086	0.482518	0.032*
C11	0.63263 (11)	0.97772 (14)	0.63494 (11)	0.0278 (3)
H11	0.568987	0.927480	0.643696	0.033*
C12	0.69928 (11)	1.06341 (14)	0.71671 (10)	0.0266 (3)
C13	0.79025 (11)	1.14236 (14)	0.70558 (11)	0.0288 (3)
H13	0.833660	1.201804	0.762731	0.035*
C14	0.81617 (11)	1.13236 (13)	0.60914 (11)	0.0266 (3)
H14	0.876936	1.187378	0.599095	0.032*

in DMF (10 mL), 4-nitrobenzyl bromide (2.16 g, 0.01 mol) and anhydrous potassium carbonate (1.38 gm, 0.01 mol) were added. The mixture was stirred at room temperature for 12 h after which water (15 mL) was added and the mixture stirred for further 30 min at room temperature. The precipitated crude product was filtered, washed with cold water, dried and crystallized from its ethanol solution to yield 2.78 g (88%) of (I) as transparent blocks. M.pt.: 465–467 K (uncorrected). ¹H NMR (DMSO-d₆, 500.13 MHz): δ 1.18 (t, 3H, CH₃, *J* = 7.5 Hz), 2.67 (q, 2H, CH₂, *J* = 7.5 Hz), 4.60 (s, 2H, CH₂S), 7.71 (d, 2H, Ar–H, *J* = 8.5 Hz), 8.18 (d, 2H, Ar–H, *J* = 8.5), 13.66 (s, 1H, NH). ¹³C{¹H} NMR (DMSO-d₆, 125.76 MHz): δ 12.22 (CH₃), 29.98 (CH₂), 33.58 (CH₂S), 95.87 (pyrimidine C-5), 115.24 (CN), 123.97, 130.76, 145.88, 147.14

(Ar–C), 162.40 (pyrimidine C-2), 167.0 (pyrimidine C=O), 178.82 (pyrimidine C-4). ESI–MS (*m/z*): 315.2 [M–H]⁺.

Experimental details

The C-bound H atoms were geometrically placed (C–H = 0.95–0.99 Å) and refined as riding with $U_{iso}(H) = 1.2$ or $1.5U_{eq}(C)$. The N-bound H atom was located in a difference map and refined with N–H = 0.88 ± 0.01 Å, and with $U_{iso}(H) = 1.2U_{eq}(N)$.

Comment

Pyrimidine heterocycles and related derivatives such as uracil, thymine and cytosine represent the cores of several potent chemotherapeutic agents [6]. The chemotherapeutic efficacy of pyrimidine-based drugs is accredited to their inhibitory effect on the biosynthesis of pivotal enzymes responsible for the synthesis of nucleic acids such as thymidine phosphorylase, thymidylate synthetase, dihydrofolate reductase and reverse transcriptase [7]. Numerous pyrimidine-based drugs are presently used as effective anti-cancer [8, 9], anti viral [10] and anti-microbial agents [11]. The title compound, (I), was developed and investigated crystallographically in the context of recent studies into the potential of related pyrimidyl derivatives as anti-microbial agents [5] and dihydrofolate reductase inhibitors [12, 13].

The molecular structure of (I) is shown in the upper image of the figure (50% probability ellipsoids). The central sulphur atom is in a V-shaped geometry [C4–S1–C8 = 102.55(6)°] within a C₂ donor set. This is obvious, since the C4 and C8 atoms have different hybridizations. The dihedral angle between the pyrimidyl and phenyl rings is 84.11(6)°, indicative of a near to orthogonal relationship. The nitro substituent is co-planar with the ring it is connected to, forming a dihedral angle of 5.20(12)°. Globally, with reference to the substituted pyrimidyl ring, the ethyl and nitrophenyl residues lie to the same side of the molecule.

There are two literature precedents which are particularly worthy of mention, namely the *n*-propyl and 2-methylpropyl [13] analogues, whereby these groups substitute for the ethyl group in (I). While the *n*-propyl derivative is isostructural with (I), the 2-methylpropyl analogue is not. The other structure worthy of mention is one with 2-methylpropyl and 4-fluorophenyl substituents

[14] instead of the ethyl and 4-nitrophenyl substituents of (I). The literature precedents adopt molecular conformations akin to that just described for (I).

In the molecular packing of (I), hydrogen bonding of the type amide–N–H $\cdots$ O(amide) features within centrosymmetric, eight-membered $\{\cdots HNCO\}$ synthons $[N2-H2n\cdots O1^i: H2n\cdots O1^i = 1.911(12)$ Å, $N2\cdots O1^i = 2.8032(14)$ Å with angle at $H2n = 175.6(11)^\circ$ for symmetry operation (i): $2 - x, 1 - y, 1 - z]$. Chains are formed along the *b*-axis direction whereby the aforementioned rings are linked by short $S1\cdots S1^ii$ interactions of $3.2057(4)$ Å cf. with the sum of the van der Waals radii of 3.60 Å [15] for symmetry operation (ii): $2 - x, 2 - y, 1 - z$. A view of the supramolecular chain is illustrated in the lower image of the figure. Contributing to the stability of the chain are long benzyl–C–H $\cdots$ O(amide) $[C8-H8A\cdots O1^{iii}: H8A\cdots O1^{iii} = 2.56$ Å, $C8\cdots O1^{iii} = 3.4894(15)$ Å with angle at $H8A = 156^\circ$ for (iii): $x, 1 + y, z]$; these are not shown in the figure. The connections leading to a three-dimensional architecture involve the substituted pyrimidyl ring. Thus, one of the nitro–O atoms approaches the ring in a side-on fashion $[N4-O3\cdots Cg(\text{pyrimidyl})^{iv} = 2.9404(14)$ Å with angle at $O3 = 120.98(11)^\circ$ for (iv): $3/2 - x, 1/2 + y, 3/2 - z]$ as does the nitrile–N atom $[C1-N1\cdots Cg(\text{pyrimidyl})^v = 3.8321(14)$ Å with angle at $N1 = 92.53(10)^\circ$ for (v): $3/2 - x, -1/2 + y, 1/2 - z]$, but on the other side of the ring.

The supramolecular chain along the *b*-axis described for (I) also occurs in the crystals of isostructural *n*-propyl (II) and non-isostructural 2-methylpropyl (III) analogues, respectively [13]. With this in mind, it was thought of interest to compute the Hirshfeld surfaces and to evaluate the full and decomposed two-dimensional fingerprint plots for (I)–(III). This exercise was conducted with Crystal Explorer 17.5 [16] in accord with established procedures [17]. In the analysis, the major contribution to the calculated Hirshfeld surface of (I) is due to $O\cdots H/H\cdots O$ contacts at 25.4% with almost equivalent contributions from $H\cdots H$ [18.6%] and $C\cdots H/H\cdots C$ [18.5%] contacts. While the percentage contribution from $O\cdots H/H\cdots O$ contacts is rather high, most occur at separations greater than the sum of the van der Waals radii. The next most significant contributing contacts are of the type $S\cdots H/H\cdots S$ at 6.4%. The remaining contacts beyond 1.3% involve carbon, i.e. $O\cdots C/C\cdots O$ [5.8%] and $N\cdots C/C\cdots N$ [3.1%]. It is noted that despite the identification of $S\cdots S$ secondary bonding in the crystal of (I), the contribution to the overall surface is only 0.9%.

When analogous calculations were conducted for each of (II) and (III), there were significant perturbations in terms of increased participation of hydrogen in the most significant surface contacts, a correlation readily related to the increased hydrogen content for (I) < (II) < (III). This trend was most evident for the $H\cdots H$ which increased from

18.6, 20.3 and 25.8% for (I)–(III), respectively. A similar trend was evident for the $O\cdots H/H\cdots O$ contacts, i.e. 25.4, 25.4 and 27.9%, respectively. To compensate these increases, there was a small downward trend in the $N\cdots H/H\cdots N$ contacts, i.e. 13.9, 13.5 and 13.2%. Downward trends were also noted for the $N\cdots C/C\cdots N$ [3.1, 2.8 and 1.8%, respectively], and in the $O\cdots C/C\cdots O$ [5.8, 4.6 and 2.6%] contacts. Of the other contacts, the $C\cdots H/H\cdots C$ [18.5, 19.1, 16.8%] and $S\cdots H/H\cdots S$ [6.4, 6.6 and 5.9%] contacts varied in a non-systematic fashion.

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