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Crystal structure of 4-amino-*N*-(2-pyrimidinyl)benzenesulfonamide–1,4-dioxane (1/1),

$C_{14}H_{18}N_4O_4S$

Table 1: Data collection and handling.

Crystal:	Colorless block
Size:	0.25 × 0.25 × 0.24 mm
Wavelength:	Cu K α radiation (1.54184 Å)
μ :	2.13 mm ⁻¹
Diffractometer, scan mode:	Xcalibur, ω
$\theta_{\max}$, completeness:	71.6°, 99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	10,393, 10,393, n/a
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2\sigma(I_{\text{obs}})$, 8935
$N(\text{param})_{\text{refined}}$:	560
Programs:	CrysAlis ^{PRO} [1], Olex2 [2], SHELX [3]

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Abstract

$C_{14}H_{18}N_4O_4S$, triclinic, $P\bar{1}$ (no. 2), $a = 9.027(1)$ Å, $b = 10.658(1)$ Å, $c = 16.358(1)$ Å, $\alpha = 90.083(6)^\circ$, $\beta = 92.278(6)^\circ$, $\gamma = 103.085(6)^\circ$, $V = 1531.66(19)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0419$, $wR_{\text{ref}}(F^2) = 0.1175$, $T = 110.9(3)$ K.

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The asymmetric unit of the title crystal 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

4-Amino-*N*-(2-pyrimidinyl)benzenesulfonamide (30 mg, 0.12 mmol) was dissolved in a mixed solvent system of acetone and 1,4-dioxane in a ratio of 6:10 (16 ml) at room temperature. The solution was filtered, sealed, and left to stand. After two weeks, colorless and block crystals were collected through solvent evaporation.

Experimental details

Hydrogen atoms were fixed in geometrically constrained positions and treated as riding on the parent atoms with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$ [4, 5].

Comment

4-Amino-*N*-(2-pyrimidinyl)benzenesulfonamide, also known as sulfadiazine, is commonly used in clinical practice as a sulfonamide anti-infective drug. It has an inhibitory effect on sensitive bacteria and microorganisms, such as plasmodium, actinomycetes, and toxoplasma gondii, and is particularly effective in treating epidemic meningitis. However, sulfadiazine powder has poor properties, such as small particle size, poor fluidity, and low bulk density [6], which affect its solubility and preparation processes, such as tableting. Changing crystallization mode is a way to improve the properties of the powder but is ineffective in controlling crystal habit and particle size. Thus,

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

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
S1	0.70055 (5)	0.76559 (4)	−0.02130 (3)	0.01230 (13)
O1	0.83651 (15)	0.86711 (14)	−0.02257 (8)	0.0171 (3)
O2	0.69737 (16)	0.66355 (13)	0.03622 (8)	0.0173 (3)
N1	0.32800 (19)	0.87896 (15)	0.00767 (9)	0.0140 (3)
N2	0.36910 (19)	0.66512 (16)	0.00348 (10)	0.0152 (3)
N3	0.56958 (19)	0.84546 (16)	−0.00126 (10)	0.0150 (3)
N4	0.5857 (2)	0.5395 (2)	−0.35366 (11)	0.0281 (4)
C1	0.1800 (2)	0.8302 (2)	0.01505 (11)	0.0161 (4)
C2	0.1187 (2)	0.6987 (2)	0.01865 (12)	0.0181 (4)
C3	0.2200 (2)	0.62005 (19)	0.01153 (12)	0.0171 (4)
C4	0.4160 (2)	0.79264 (18)	0.00352 (10)	0.0130 (4)
C5	0.6583 (2)	0.69942 (18)	−0.11967 (11)	0.0129 (4)
C6	0.5817 (2)	0.57095 (19)	−0.12994 (12)	0.0143 (4)
C7	0.5559 (2)	0.5185 (2)	−0.20808 (12)	0.0175 (4)
C8	0.6052 (2)	0.5938 (2)	−0.27684 (12)	0.0181 (4)
C9	0.6784 (2)	0.7241 (2)	−0.26533 (12)	0.0189 (4)
C10	0.7052 (2)	0.7767 (2)	−0.18750 (12)	0.0161 (4)
S2	0.80284 (5)	0.73578 (4)	0.46990 (3)	0.01199 (13)
O3	0.66526 (16)	0.63589 (14)	0.46025 (8)	0.0171 (3)
O4	0.80708 (16)	0.83199 (13)	0.53211 (8)	0.0169 (3)
N5	1.13583 (19)	0.83277 (16)	0.50015 (10)	0.0145 (3)
N6	1.17464 (19)	0.61817 (16)	0.50330 (10)	0.0145 (3)
N7	0.93310 (19)	0.65333 (16)	0.49030 (10)	0.0144 (3)
N8	0.9288 (2)	0.9920 (2)	0.15291 (11)	0.0247 (4)
C11	1.2865 (2)	0.87710 (19)	0.50864 (12)	0.0165 (4)
C12	1.3878 (2)	0.7971 (2)	0.51571 (12)	0.0178 (4)
C13	1.3243 (2)	0.6661 (2)	0.51213 (12)	0.0167 (4)
C14	1.0878 (2)	0.70482 (18)	0.49824 (11)	0.0133 (4)
C15	0.8453 (2)	0.81120 (18)	0.37639 (11)	0.0126 (4)
C16	0.9121 (2)	0.94203 (19)	0.37439 (11)	0.0139 (4)
C17	0.9409 (2)	1.00187 (19)	0.29988 (12)	0.0163 (4)
C18	0.9031 (2)	0.9312 (2)	0.22590 (12)	0.0168 (4)
C19	0.8399 (2)	0.7980 (2)	0.22960 (12)	0.0185 (4)
C20	0.8108 (2)	0.73825 (19)	0.30374 (12)	0.0156 (4)
O5	0.3965 (2)	0.80037 (16)	0.18729 (10)	0.0296 (4)
O6	0.3588 (2)	0.94760 (17)	0.32547 (10)	0.0309 (4)
C21	0.4937 (3)	0.9234 (3)	0.20434 (15)	0.0287 (5)
C22	0.5051 (3)	0.9507 (3)	0.29524 (15)	0.0336 (6)
C23	0.2598 (3)	0.8258 (3)	0.30770 (14)	0.0298 (5)
C24	0.2504 (3)	0.7973 (3)	0.21728 (14)	0.0304 (5)
O7	0.92768 (18)	0.28278 (16)	0.18253 (9)	0.0248 (3)
O8	0.8340 (2)	0.43373 (16)	0.30382 (10)	0.0313 (4)
C25	1.0058 (3)	0.4131 (2)	0.19764 (14)	0.0248 (5)
C26	0.9901 (3)	0.4503 (2)	0.28561 (15)	0.0300 (5)
C27	0.7564 (3)	0.3039 (2)	0.28844 (14)	0.0244 (5)
C28	0.7718 (3)	0.2667 (3)	0.20069 (14)	0.0283 (5)
H16	0.937 (3)	0.983 (2)	0.4224 (14)	0.009 (5)*
H2	0.015 (3)	0.667 (3)	0.0246 (15)	0.023 (6)*
H13	1.383 (3)	0.607 (3)	0.5155 (15)	0.019 (6)*
H6	0.551 (3)	0.524 (3)	−0.0862 (15)	0.018 (6)*
H11	1.317 (3)	0.966 (3)	0.5105 (16)	0.024 (7)*
H3	0.595 (3)	0.926 (3)	−0.0056 (17)	0.030 (7)*
H1	0.124 (3)	0.888 (3)	0.0191 (15)	0.023 (7)*
H20	0.772 (3)	0.655 (3)	0.3058 (14)	0.018 (6)*
H19	0.815 (3)	0.752 (3)	0.1847 (16)	0.018 (6)*

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
H27A	0.800 (3)	0.252 (3)	0.3276 (16)	0.024 (6)*
H7A	0.903 (3)	0.576 (3)	0.4890 (15)	0.020 (6)*
H12	1.491 (3)	0.825 (3)	0.5220 (15)	0.021 (6)*
H10	0.749 (3)	0.860 (3)	−0.1793 (15)	0.021 (6)*
H17	0.983 (3)	1.092 (3)	0.2954 (15)	0.020 (6)*
H23A	0.298 (3)	0.762 (3)	0.3333 (16)	0.024 (7)*
H7	0.503 (3)	0.428 (3)	−0.2150 (15)	0.019 (6)*
H8A	0.912 (4)	0.952 (3)	0.109 (2)	0.035 (8)*
H3A	0.185 (3)	0.529 (3)	0.0152 (16)	0.025 (7)*
H9	0.710 (4)	0.777 (3)	−0.3113 (18)	0.035 (8)*
H25A	1.111 (3)	0.420 (3)	0.1876 (15)	0.023 (6)*
H23B	0.158 (4)	0.821 (3)	0.3258 (18)	0.035 (8)*
H4A	0.616 (4)	0.584 (3)	−0.3955 (19)	0.034 (8)*
H8B	0.959 (3)	1.071 (3)	0.1516 (17)	0.029 (7)*
H22A	0.543 (3)	0.879 (3)	0.3200 (17)	0.031 (7)*
H26A	1.043 (4)	0.400 (4)	0.321 (2)	0.042 (9)*
H25B	0.962 (3)	0.470 (3)	0.1613 (17)	0.027 (7)*
H28A	0.722 (3)	0.316 (3)	0.1645 (17)	0.029 (7)*
H27B	0.654 (3)	0.294 (3)	0.3020 (16)	0.027 (7)*
H21A	0.460 (4)	0.989 (3)	0.1786 (18)	0.037 (8)*
H26B	1.037 (4)	0.537 (3)	0.2959 (18)	0.036 (8)*
H21B	0.599 (4)	0.918 (3)	0.1862 (18)	0.036 (8)*
H24A	0.206 (4)	0.871 (4)	0.191 (2)	0.048 (9)*
H28B	0.724 (4)	0.181 (3)	0.1904 (18)	0.037 (8)*
H4B	0.516 (4)	0.470 (3)	−0.3636 (17)	0.032 (7)*
H24B	0.185 (4)	0.717 (4)	0.206 (2)	0.048 (9)*
H22B	0.570 (4)	1.034 (4)	0.306 (2)	0.046 (9)*

sulfadiazine polymorphism screening has attracted interest [7]. Sulfadiazine solvate formation is convenient for controlling particle size and crystal habit. Different desolvent conditions may cause different crystalline phases, which are beneficial to the improvement of sulfadiazine production properties [8–11]. Preparing sulfadiazine through phase conversion mediation is expected to improve the poor properties. Currently, reports on sulfadiazine crystal forms are rare. The crystal data include active pharmaceutical ingredients, metal complexes, solvates and cocrystals [12, 13]. Solvates have been reported, namely: 4-methylpyridine solvate, *N,N*-dimethylacetamide solvate, *N*-alkylpyrrolidone solvate, tetrahydrofuran solvate, and 1,4-dioxane solvate, which mostly have nitrogen/oxygen-containing ring structures, so do cocrystal formers [8, 14–19]. However, 1,4-dioxane solvate lacks single-crystal data. In this study, we finally acquired 1,4-dioxane solvate of sulfadiazine through two weeks of slow evaporation in a mixed solvent of acetone and 1,4-dioxane.

The crystal was measured and analyzed. It presented a twinning phenomenon. The ratio of major and minor

components is 0.5841(9):0.4159(9). The results showed the 1,4-dioxane solvate of sulfadiazine crystallized in the triclinic space group $P\bar{1}$ and consisted of four formula units per unit cell ($Z = 4$). Every asymmetry unit has sulfadiazine and 1,4-dioxane molecules in a ratio of 1:1, as presented in the Figure. Thus, the asymmetric unit contains two sulfadiazine and two 1,4-dioxane molecules, and sulfadiazine molecules have the same conformation. Sulfadiazine has the dihedral angle of 99° . The crystals maintain intermolecular interactions owing to hydrogen bonds and van der Waals forces. Six hydrogen bonds ($N_4 \cdots O_3$ ($x, y, z - 1$): 3.269(2) Å; $N_4 \cdots O_3(-x + 1, -y + 1, -z)$: 3.070(2) Å; $N_3 \cdots N_1(-x + 1, -y + 2, -z)$: 2.876(2) Å; $N_7 \cdots N_6(-x + 2, -y + 1, -z + 1)$: 2.840(2) Å; $N_8 \cdots O_1$: 3.163(2) Å; $N_8 \cdots O_7$ ($x, y + 1, z$): 3.139(3) Å) exist between sulfadiazine molecules. All hydrogen bonds lengths are in the expected ranges. One hydrogen bond ($N_{4sul} \cdots O_{3sul}$: 3.269(2) Å) of a dimeric motif $D_1^1(2)$ forms between an amino group and a sulfonyl group. The secondary amine group and pyrimidinyl group is linked to a symmetry related one ($N_3 \cdots N_1$: 2.876(2) Å; $N_7 \cdots N_6$: 2.840(2) Å; dimer ring motif $R_2^2(8)$). No hydrogen bonds are present between sulfadiazine and 1,4-dioxane unlike other solvates, showing intermolecular hydrogen bond $N_{sul} \cdots O/N_{solvate}$ between the amino group in sulfadiazine and oxygen/nitrogen atom in solvate molecules [8]. The title 1,4-dioxane solvate of sulfadiazine presents a net structure and is mainly held by hydrogen bonds $N-H \cdots O/N$ between sulfadiazine molecules. Every sulfadiazine molecule can interact with two neighboring sulfadiazine molecules. The 1,4-dioxane molecules are filled in channels between sulfadiazine molecules, which facilitates the desolvent process.

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