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Structure of 4-amino-3-butyl-1,2,4-triazole-5-thione: Relation to derivatives with H, Me, Et, and Pr in the 3-position

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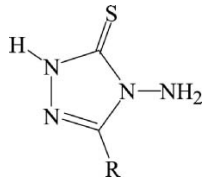
The compound 4-amino-3-butyl-1,2,4-triazole-5-thione [crystal data: $C_6H_{12}N_4S$, triclinic, $P\bar{1}$, $Z=2$, $a=7.546(2)$, $b=11.217(3)$, $c=5.681(1)$ Å, $\alpha=103.12(2)$, $\beta=91.33(2)$, $\gamma=72.41(2)^\circ$, $V=445.9(2)$ Å^3] contains an essentially planar triazole ring with the butyl group rotated out of the plane by approximately 104°. The molecules form hydrogen-bonded dimers through intermolecular N–H···S interactions involving the thione sulfur atom and the protonated nitrogen atom on the ring. These units are then linked into columns through N–H···N hydrogen bonds between the amine group and the unsubstituted ring N atom of adjacent molecules. The structural features of this compound are compared with those of the corresponding triazoles with H, methyl, ethyl and propyl groups on the 3-carbon.

KEY WORDS: Triazole; thione-substituted triazole; amine-substituted triazole.

Introduction

Heterocyclic compounds, including triazoles, have been found to possess wide-ranging biological activities, finding application as antibacterial, antiviral, antifungal and anti-inflammatory agents.[1–4] As part of a continuing study of the structural characteristics of amine- and thione-substituted triazoles[5,6] (Scheme 1) and their metal complexes,[7,8] we have structurally characterized the compound 4-amino-3-butyl-1,2,4-triazole-5-thione. This now completes a series with $R=H$,[7] CH_3,[9] C_2H_5,[10] C_3H_7,[7] and C_4H_9, permitting a systematic comparison of the effect of the R group on the crystal and molecular structure of this family of compounds.



Scheme 1. Chemical structure of 4-amino-3-*R*-1,2,4-triazole-5-thione.

Experimental

Synthesis and spectroscopic characterization

To prepare the compound in bulk, 10.0 g (0.0943 mol) of thiocarbohydrazide (Aldrich, 98%) was heated in 30 mL of refluxing pentanoic acid (Aldrich, 99%) for 5 h at 80–90°C. Following

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this, approximately 5 mL of the solvent was distilled off while maintaining the temperature below 90° (higher temperatures were found to decompose the product). The pale-yellow solution was then allowed to stand at room temperature for 3 days during which time 7.36 g (45% yield) of the product crystallized out as an off-white solid. It was characterized by melting range (75–83°), mass spectrometry (*m/z* (M^+) 172), NMR [^{1}H (d_6–DMSO), ppm (referenced to DMSO 2.49 ppm): δ 0.86 (triplet, 3H, CH_3), 1.31 (sextet, 2H, CH_2), 1.59 (quintet, 2H, CH_2), 2.60 (triplet, 2H, CH_2), 5.49 (singlet, 2H, NH_2), 13.40 (broad singlet, 1H, NH);^{13}C{^{1}H} (d_6–DMSO), ppm (referenced to DMSO 39.5 ppm): δ 13.55, 21.59, 23.89, 27.58 (butyl carbons), 152.2 and 165.7 (ring carbons)], and IR [reported in cm^{-1} with relative intensities as very strong, strong, medium or weak in parentheses; 3322 (m), 3148 (s), 2961 (s), 2931 (s), 2870 (m), 1621 (m), 1565 (m), 1487 (vs), 1451 (m), 1376 (w), 1337 (m), 1314 (w), 1290 (w), 1114 (w), 1033 (w), 959 (w), 937 (m), 920 (w), 734 (w), 547 (w)]. X-ray quality crystals were obtained from the initial product without further recrystallization.

Crystallographic study

The single-crystal X-ray diffraction measurements were done at room temperature on a Rigaku AFC6S four-circle diffractometer (graphite monochromated sealed tube Mo Kα X-ray source; $\lambda = 0.7107$ Å) operated by the MSC-AFC Diffractometer Control software.[11] Data collection details are provided in Table 1. All crystallographic calculations were performed on a VAXStation 3100/76 computer with the teXsan[12] series of programs. The structure was solved by direct methods (MITHRIL[13]). Hydrogen atoms were located on difference electron density maps and their positions refined with the U_{iso} value of each H atom fixed at 1.2 times the U_{eq} value of the attached atom at the time of its inclusion. Structural diagrams were generated using the CrystalMaker[14] program.

Table 1. Crystallographic Data for 4-Amino-3-Butyl-1,2,4-Triazole-5-Thione

Compound	$C_6H_{12}N_4S$
CCDC no.	274748
Color/shape	Colorless/block
Empirical formula	$C_6H_{12}N_4S$
Formula weight	172.25
Temperature (K)	296
Crystal system	triclinic
Space group	$P\bar{1}$
a (Å)	7.546(2)
b (Å)	11.217(3)
c (Å)	5.681(1)
α (°)	103.12(2)
β (°)	91.33(2)
γ (°)	72.41(2)
Volume (Å^3)	445.9(2)
Formula units/cell (Z)	2
Dcalc (g cm^{-3})	1.283
μ (cm^{-1})	3.08
Transmission factors	0.885–0.957
Diffractometer/scan	Rigaku AFC6S/ω–2θ scans
θ range for data (°)	1.95–25.00
Reflections measured	1702 ($+h$, $\pm k$, $\pm l$)
Independent/observed reflns	1572 ($R_{int} = 0.029$)/1113 [$I > 3\sigma(I)$]
Data/restraints/parameters	1113/0/136
Goodness of fit	2.08
R indices (R; wR)	0.0347; 0.0327

Results and discussion

The molecular structure with numbering scheme is shown in Fig. 1. The molecule exists as the thione tautomer in the solid state, with the proton (H3) on the nitrogen atom adjacent to the C = S group. This is consistent with all of the other members of this family of triazoles.[7,9,10,15] The ring is essentially planar (maximum deviation 0.0103(25) Å, $\chi^2 = 39.8$) and the S, N1 and C3 atoms are all within 0.05 Å of the plane. The geometry within the ring (Table 2) is similar to that found in the related compounds. The C4, C5, and C6 atoms are 1.41, 1.47, and 2.80 Å out of the plane as the butyl group is rotated away from the plane [torsion angle: N4–C2–C3–C4 104.2(3)°], however, the carbon chain adopts an ideal *anti*-conformation [torsion angles: C2–C3–C4–C5 178.5(2)° and C3–C4–C5–C6 –175.9(3)°]. The molecules associate *via*

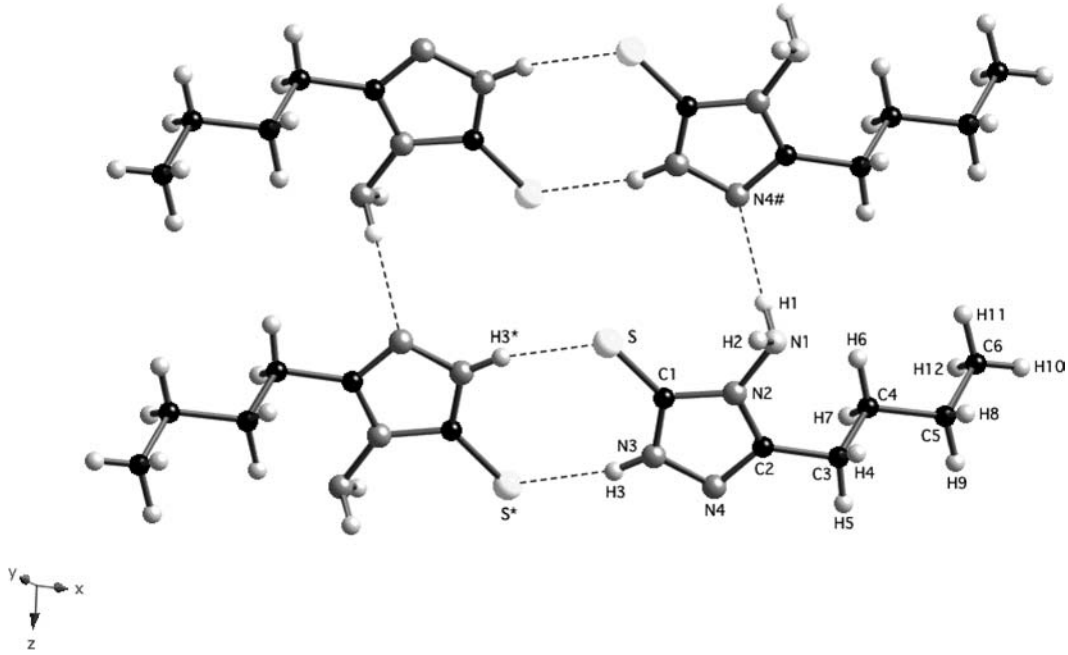

Fig. 1. Diagram of the molecular structure of 4-amino-3-butyl-1,2,4-triazole-5-thione showing atom labeling scheme. Symmetry equivalent molecules have been included to show the intramolecular N–H···S and N–H···N hydrogen bonding [symmetry operations (#): $x, y, z-1$; (*): $-x, 2-y, 2-z$].

relatively long N–H···S hydrogen bonds (Table 3) across centers of inversion, leading to a dimerization that is similar to that found in the related family of 1-*R*-imidazole-2-thiones[16–18] and is analogous to the hydrogen bonding found in carboxylic acids, although weaker. The dimers are linked in the *z* direction by N–H···N hydrogen bonds (Table 3) between the amine group of one molecule and the unsubstituted and unprotonated triazole N atom (N4) of the neighboring molecule. The result is columns of hydrogen-bonded molecules running along the *c* axis that effectively pack in layers with the butyl groups side-by-side (Fig. 2).

Table 2. Selected Bond Distances (Å) and Angles (°)

Bond distances (Å)	
S–C1	1.674(2)
N1–N2	1.399(3)
N2–C1	1.379(3)
N2–C2	1.365(3)
N3–N4	1.389(3)
N3–C1	1.337(3)
N4–C2	1.307(3)
Bond angles (°)	
N1–N2–C1	126.8(2)
N1–N2–C2	123.7(2)
C1–N2–C2	109.5(2)
N4–N3–C1	113.9(2)
N3–N4–C2	103.7(2)
S–C1–N2	127.3(2)
S–C1–N3	130.3(2)
N2–C1–N3	102.3(2)
N2–C2–N4	110.6(2)
N2–C2–C3	124.2(2)
N4–C2–C3	125.2(2)

As it turns out the exact intermolecular interactions and packing patterns are different for most of the members of the series, as well as the related 3-trifluoromethyl derivative.[8] Unit cell parameters and space groups are shown in Table 4 for comparison. Of the other alkyl-substituted triazole compounds, only the 3-ethyl derivative[10] also forms inversion-related N–H···S dimers like those seen in the present work linked into chains by the N–H···N hydrogen bonds. The latter interactions are noticeably longer (H···N distance 2.65 Å) in the ethyl compound. Also, the molecules do not pack with the pendant ethyl groups segregated like the butyl groups.

Table 3. Hydrogen Bonding Interactions (Å, °).

D	H	A	*d*(D–H)	*d*(H···A)	*d*(D···A)	Angle(D–H···A)	Symmetry operation
N1	H1	N4	0.83(3)	2.43(3)	3.251(3)	173(3)	$x, y, z-1$
N3	H3	S	0.88(2)	2.53(3)	3.369(3)	160(2)	$-x, 2-y, 2-z$

Evidently, the additional contacts of the longer alkyl groups are sufficiently favorable to make this a dominant feature of the packing in the 3-butyl derivative. Of note, the 3-phenyl compound[15] also displays this type of hydrogen bonding network in space group $P\bar{1}$. It is like the ethyl compound in that the molecules are positioned so that the *R* groups are not segregated from the triazole rings. The 3-perfluoromethyl derivative[8] has a similar network of intermolecular interactions as found in the butyl compound, namely N–H···S interactions leading to dimerization, further connection into chains by N–H···N (amine···ring) hydrogen bonds, and stacking of the chains to give alternating layers of rings and perfluoromethyl groups. A major difference is that the 3-perfluoromethyl molecules in the dimer are not related by the center of inversion. Rather, the

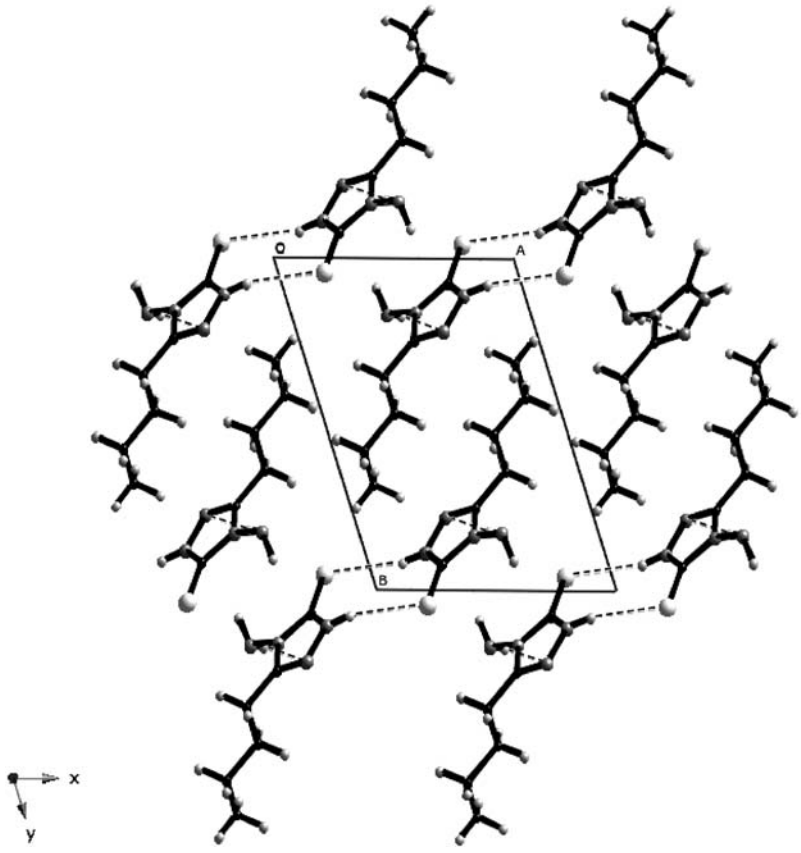

Fig. 2. Packing diagram of 4-amino-3-butyl-1,2,4-triazole-5-thione showing the outline of the unit cell. View is along the *c* axis. Hydrogen bonds are shown as dashed lines.

Table 4. Unit Cells and Space Groups for 4-Amino-3-*R*-1,2,4-Triazole-5-Thione Compounds.

$R =$	H[7]	CH_3[9]	CF_3[8]	C_2H_5[10]	C_3H_7[7]	C_4H_9
Space group	*C*2/*c*	*Pbcm*	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
a (Å)	21.169(6)	8.877(4)	8.455(6)	7.382(8)	11.358(2)	7.546(2)
b (Å)	14.326(5)	9.813(2)	13.688(6)	7.520(2)	9.804(3)	11.217(3)
c (Å)	6.954(4)	6.545(2)	6.369(4)	6.681(3)	6.805(2)	5.681(1)
α (°)	90	90	95.99(5)	108.05(3)	90	103.12(2)
β (°)	103.59(5)	90	105.37(5)	104.61(7)	90.34(2)	91.33(2)
γ (°)	90	90	97.46(5)	96.15(5)	90	72.41(2)
V (Å^3)	2050(2)	570.1(5)	697.2(8)	334.2(4)	757.8(3)	445.9(2)
Z	16	4	4	2	4	2

participating molecules are crystallographically independent and the bonding is unsymmetrical (S···H distances 2.24 and 2.51 Å).

The molecules in the 3-propyl compound[7] are linked by N–H···S hydrogen bonds involving the protonated ring nitrogen atom, however the interactions are not related by inversion. Rather, the S and H atoms on a given molecule interact with different molecules related by the 2_1 axis. Thus, this interaction leads directly to chains (along *b*), rather than dimers. There is also no N–H···N hydrogen bond with H···N less than 3.0 Å in this structure. It does follow the butyl derivative, however, in that the rings and propyl groups are segregated. The 3-methyl derivative[9] is very similar in its packing to the propyl derivative. Both have chains of molecules linked by N–H···S interactions with the *R* groups in between. This makes sense in that the space group of the methyl compound, *Pbcm*, is a minimal non-isomorphous supergroup of the space group of the propyl compound, $P2_1/c$. Comparison of the unit cells (Table 4) shows that the *b* and *c* axes are almost the same (and $\beta \approx 90°$ for the monoclinic cell), while the *a* axis is longer for the propyl compound since this corresponds to the direction of the *R* groups. Taken together, the $R =$ methyl, ethyl, propyl, and butyl structures are reminiscent of the old patterns of compounds containing alkyl chains showing correlations based on the odd or even chain lengths of the alkyl groups. The compound with $R = H$[7] is unique in this series in that it displays only N–H···N hydrogen bonding (involving both the amine and ring N atoms) and an unusual pattern of hollow circular columns of molecules with voids of greater than 4.0 Å in the center.

These structures demonstrate very clearly the significant effect that a small change in the size of one functional group can have on the hydrogen bonding pattern and overall crystal packing in a series of related molecules.

Supplementary material CCDC file 274748 contains the supplementary crystallographic data for the structure reported in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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