

Full Paper

Synthesis and Molecular Structure of 6-Amino-3-benzylmercapto-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one

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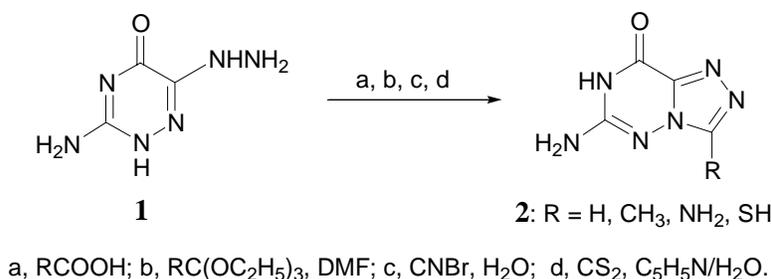
Abstract: The title compound 6-amino-3-benzylmercapto-1,2,4-triazolo[3,4-*f*][1,2,4]-triazin-8(7*H*)-one (**4**), molecular formula C₁₁H₁₀N₆OS, was obtained by the reaction of 3-amino-2-benzyl-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**3**) with carbon disulfide in a water/pyridine mixture. Compound **4** can also be synthesized by reacting 6-amino-3(2*H*)mercapto-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**7**) with benzyl bromide in methanolic ammonia water. The compound crystallizes in the monoclinic space group *P*2₁/*c* with *a* = 7.2926(15), *b* = 14.456(2), *c* = 11.436(2) Å, β = 105.30(2)°, *V* = 1162.9(4) Å³ and *Z* = 4, resulting in a density *D*_{calc} of 1.567 g/cm³. Molecules of **4** are linked by extensive intermolecular N-H⋯N and N-H⋯O hydrogen bonding [graph set R₂²(9)]. The structure is further stabilized by π-π stacking interactions.

Keywords: 1,2,4-Triazine, 1,2,4-triazolo[3,4-*f*][1,2,4]triazine, X-ray crystal structure, hydrogen bonds.

Introduction

1,2,4-Triazines and their condensed derivatives form an important class of heteroaromatic compounds with various biochemically interesting properties and pharmacologically significant activities [1-2]. We have recently explored the mechanism of the cyclization of the monocyclic compound 3-amino-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**1**) to form the heterobicyclic 6-amino-3-substituted-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-ones **2** [3]. This convenient reaction of **1** to afford **2** (Scheme 1) had been previously described by Lovelette [4]. As a part of our ongoing program, the compound 3-amino-2-benzyl-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**3**) was treated with a variety of one-carbon fragment reagents (formic acid, glacial acetic acid or cyanogen bromide) and no cyclization was observed [5]. In this paper we report an unexpected ring closed product **4** obtained when compound **3** is treated with carbon disulfide. As we know, many aza/deaza analogues of purine have attracted considerable interest due to their biological activities. Compound **4** contains a 6-amino-1,2,4-triazolo- [3,4-*f*][1,2,4]triazin-8(7*H*)-one moiety (4,8-diaza-9-deazaguanine), which is an isosteric isomer of guanine. In the last decade numerous fused 1,2,4-triazines have been synthesized and screened *in vitro*, revealing their anti-HIV and anti-cancer activities [6-13]. Meanwhile, fused 1,2,4-triazoles have acquired considerable importance because of their CNS depressant, anti-allergy, anti-inflammatory and antimicrobial properties [14-17]. However, the 3-substituted derivatives of 6-amino-1,2,4-triazolo- [3,4-*f*][1,2,4]triazin-8(7*H*)-one have seldom been reported.

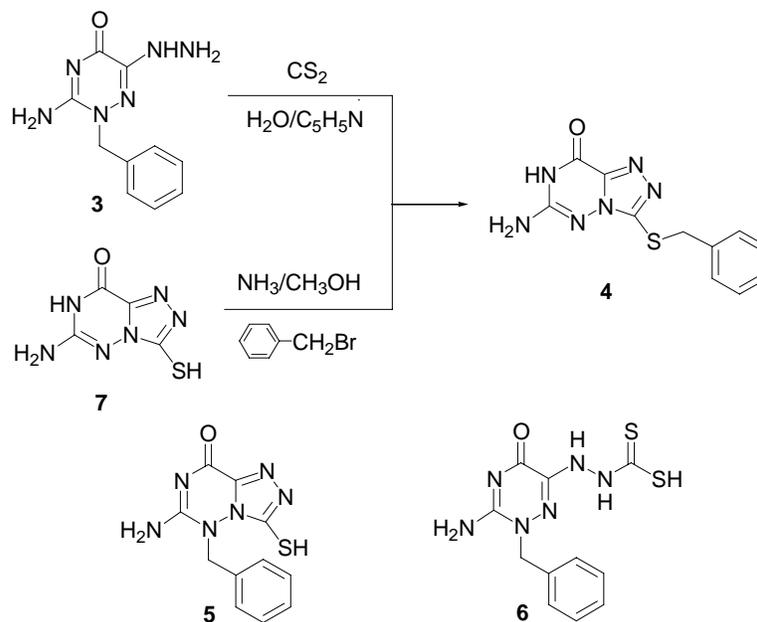
Scheme 1



Results and Discussion

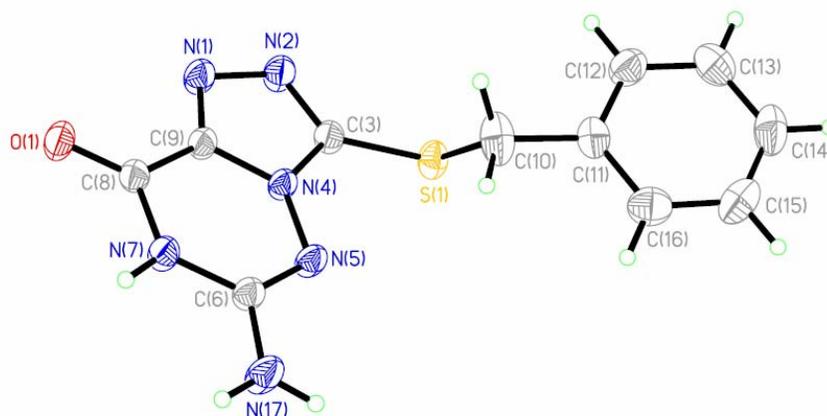
When compound **3** was refluxed with carbon disulfide in a 1:1 water/pyridine mixture an unexpected ring closed product **4** was obtained (Scheme 2). An intense IR absorption at 1735 cm⁻¹ suggested the carbonyl absorption of fused triazines and confirmed the occurrence of ring closure [3,4,18]. The ¹H-NMR spectrum showed two singlets at δ_H 4.50 and 6.50 ppm, corresponding to the benzyl group methylene protons and the 6-amino group, respectively. The remaining multiplets at δ_H 7.30 to 7.37 ppm were attributed to the aromatic protons of the benzyl group, while the broad singlet at δ_H 11.61 ppm corresponded to the NH proton of the 1,2,4-triazinone ring amide. The location of the 3-benzylmercapto group of **4** at C-3 was established by 2D-NMR. The long-range ¹H-¹³C heteronuclear correlation (HETCOR) NMR revealed the connectivity of the methylene protons (δ_H 4.50 ppm) on the benzyl group to C-3 (δ_C 144.86 ppm) in the 1,2,4-triazolo ring. Additional supporting evidence for **4** was found in the high-resolution mass spectrum showing the molecular ion at m/z 274.0635, confirming the precise molecular formula as C₁₁H₁₀N₆OS (calcd. 274.0637).

Scheme 2



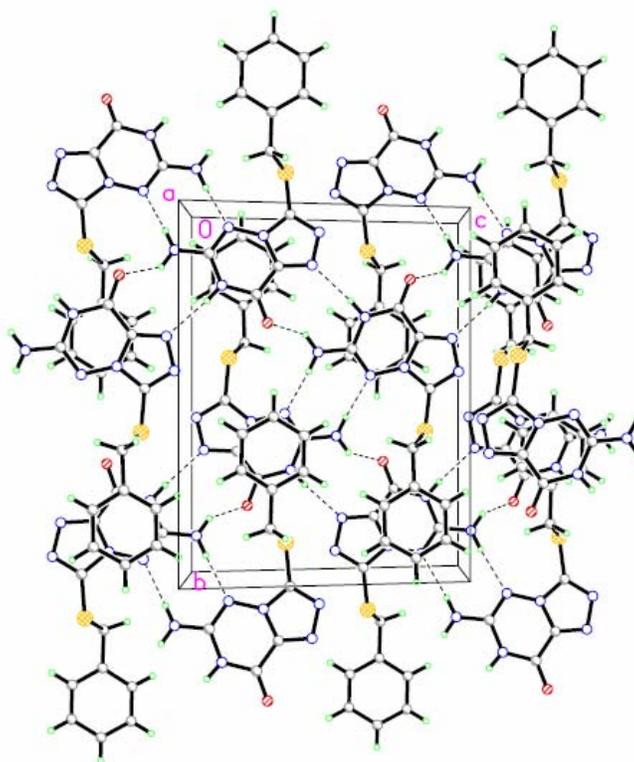
Further confirmation of the structure of product **4** was obtained from its synthesis *via* an alternative approach, by reacting 6-amino-3(2*H*)mercapto-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**7**) with benzyl bromide in methanolic ammonia (Scheme 2). The resulting nucleophilic substitution product was a material identical in every respect with compound **4**. Finally, the structure of **4** was unambiguously confirmed by X-ray crystallography, revealing the structural framework as a 1,2,4-triazole five-membered ring fused at C(9)-N(4) with a 1,2,4-triazine six-membered ring (Figure 1). The most contributing prototropic tautomerism of **4** is the amino-oxo form 7*H*-tautomer (not the 5*H*-tautomer), similar to the tautomerism of 6-amino-3-ethyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one, as previously reported by us [19]. The benzylmercapto group was substituted at C-3 showing an exoextensibility. Taken together, **4** was assigned as 6-amino-3-benzylmercapto-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one. The ring closed compound **5** and the hydrazinecarbodithioic acid compound **6** were not observed (Scheme 2).

Figure 1. ORTEP drawing and atom labelling scheme of the compound **4** with thermal ellipsoids drawn at the 50% probability level.



The ORTEP drawing for the title compound is depicted in Figure 1. The molecular packing is shown in Figure 2. In the structure of **4** the short bonds 1.310(2) Å (N(5)-C(6)), 1.320(2) Å (N(1)-C(9)) and 1.325(2) Å (N(2)-C(3)) have an appreciable double-bond character. The bond lengths 1.732(2) Å of C(3)-S(1) and 1.214(2) Å of C(8)-O(1) are shorter than the bond lengths of *Car*-S(2) (1.773 Å) and *Csp*²=O(1) (1.240 Å) in δ -lactams [20], respectively. These may be attributed to the electron abstraction by the π -deficient heterobicyclic ring. The bond length 1.340(2) Å between C(6)-N(17) is shorter than 1.355 Å of *Car*-NH₂ (*Nsp*²: planar) [20]. Meanwhile, the 119.15(15) value of the N(5)-C(6)-N(17) angle, close to 120°, confirms the *sp*² hybridization of the nitrogen atom, which suggests that the 6-amino group strongly donates the unpaired electrons and resonates with the [1,2,4]triazolo[3,4-*f*][1,2,4]triazine ring. The mean plane of 1,2,4-triazolo[3,4-*f*][1,2,4]triazine ring forms a dihedral angle of 20.27° with the benzyl group benzene ring.

Figure 2. A perspective drawing of the packing arrangement of compound **4**. Dashed lines are intermolecular N-H...N and N-H...O hydrogen bonds.



Analysis of the molecular packing in the unit cell reveals that each molecule is linked with two other molecules by intermolecular hydrogen bonds (Figure 3 and Table 1). Each title molecule is linked into two $R_2^2(9)$ graph set associations (Figure 3, notation [a], [d] and [b], [c]), each *via* one N-H...N hydrogen bond and one N-H...O hydrogen bond. Assignment of the H-bond descriptors is based on the graph-set theory [21]. The structure is further stabilized by π - π stacking (Figure 3 notation [e]) interactions, which results in the centroid...centroid distance (3.695 Å) being that between the benzene ring of the molecule at x, y, z and the 1,2,4-triazine ring of the molecule at $1-x, 0.5+y, 1.5-z$ (iii) ([e]). Molecular graphics and hydrogen bond geometry were obtained using the program Mercury (version 1.4, CCDC, Cambridge, UK).

Figure 3. A part of the crystal structure of the title compound, showing the molecule stacking (notation [e]) direction along the *a*-view. Broken lines indicate the intermolecular hydrogen bonding patterns. For notation and symmetry codes see Table 1.

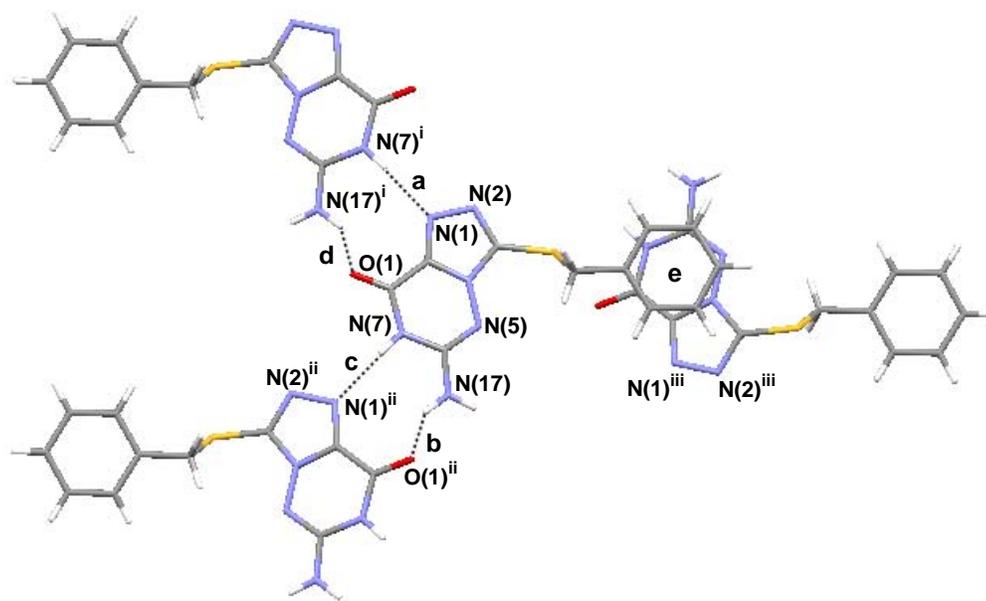


Table 1. Hydrogen bond geometry in compound 4

Notation	D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	Length-VdW	D-H...A (°)
a	N(7)-H(7A) ⁱ ...N(1)	0.860	2.104	2.961	-0.646	173.94
b	N(17)-H(17B)...O(1) ⁱⁱ	0.860	2.311	2.976	-0.409	134.34
c	N(7)-H(7A)...N(1) ⁱⁱ	0.860	2.104	2.961	-0.646	173.94
d	N(17)-H(17B) ⁱ ...O(1)	0.860	2.311	2.976	-0.409	134.34

*Note. symmetry codes: (i) $x, -0.5-y, -0.5+z$; (ii) $x, -0.5-y, 0.5+z$; (iii) $1-x, 0.5+y, 1.5-z$.

Conclusions

We have synthesized the title compound **4**, an unexpected ring closed product resulting from a reaction of a heterocyclic precursor (compound **3**). The structure of **4** was clearly identified by 2D-NMR spectroscopy and unambiguously confirmed by X-ray crystallography. A reasonable mechanism for the ring cyclization of **3** to **4** is now being explored as a part of our ongoing research programs.

Acknowledgements

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Experimental

General

Melting points were determined on a YANACO micromelting point apparatus and are uncorrected. ^1H - and ^{13}C -NMR spectra (in $\text{DMSO-}d_6$, internal standard TMS) were taken on a Varian Unity 400 (400 MHz) spectrophotometer. For the assignments of signals, standard and long-range ^1H - ^{13}C heteronuclear chemical shift correlation (HETCOR) 2D NMR experiments were used. Chemical shifts are given in the δ -scale (ppm). Infrared spectra (IR) were recorded on a Perkin-Elmer FTIR 1650 spectrophotometer with KBr discs. MS and HRMS spectra were obtained on a Quattro VG-5022 spectrometer and VG 70-250S GC/MS, respectively, with an ionization potential of 70 eV. Elemental analyses (EA) were performed on a Heraeus CHN-O-Rapid elemental analyzer. 3-Amino-2-benzyl-6-hydrazino-1,2,4-triazin-5(2H)-one (**3**) and 6-amino-3-thio(2H)-1,2,4-triazolo-[3,4-f][1,2,4]triazin-8(7H)-one (**7**) were prepared according to the methods described by Hwang *et al.* [3] and Lovelette [4], respectively.

Syntheses of 6-Amino-3-benzylmercapto-1,2,4-triazolo[3,4-f][1,2,4]triazin-8(7H)-one (**4**)

Method A: Compound **3** (0.35 g, 1.5 mmol) was suspended in a 1:1 pyridine/water mixture (15 mL), then carbon disulfide (0.16 g, 2.1 mmol) was added and the mixture was refluxed for 12 hours. Evaporation of the solvent under vacuum afforded a crude solid which was recrystallized from water to give **4** (0.16 g, 44%), m.p. 229-230 °C; IR (ν_{max} , cm^{-1}): 3431, 3330, 3016, 1735 (C=O), 1630, 1404, 1099; ^1H -NMR: δ 4.50 (s, 2H, S- CH_2 - C_6H_5), 6.50 (s, 2H, NH_2), 7.30-7.37 (m, 5H, C_6H_5), 11.61 (br s, 1H, NH); ^{13}C -NMR: δ 34.79 (S- CH_2 - C_6H_5), 127.39, 128.42, 128.89, 137.24 (C_6H_5), 141.03 (C-8a), 144.86 (C-3), 150.67 (C-6), 151.59 (C-8); MS [EI]: m/z 274 (M^+ , 1), 214 (19), 197 (3), 165 (1), 106 (40), 91 (100), 77 (7), 70 (6), 65 (31); HRMS: m/z Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_6\text{OS}$: 274.0637. Found: 274.0635; Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_6\text{OS}$: C, 48.16; H, 3.67; N, 30.64. Found: C, 48.25; H, 3.77; N, 30.83.

Method B: A solution of **7** (0.27 g, 1.5 mmol) and benzyl bromide (0.26 g, 1.5 mmol) in methanolic ammonia (previously saturated at 0°C; 25 mL) was stirred at room temperature in a sealed flask for 24 hours. Evaporation of the solvent on a vacuum evaporator and recrystallization of the residue from water afforded 251 mg (61%) of a material identical in every respect with compound **4** prepared by Method A.

X-ray techniques

X-ray quality crystals of the colorless title compound **4** were obtained by crystallization from dimethyl sulfoxide. Crystal and experimental data are summarized in Table 2. The data were collected with a NONIUS CAD4 automated diffractometer equipped with a graphite-monochromatized Mo K_α radiation ($\lambda = 0.71073\text{\AA}$) at 295(2) K. The crystal structure data have been deposited at the Cambridge Crystallographic Data Centre [22]. The unit-cell parameters were determined from 25 reflections with $8.75^\circ \leq 2\theta \leq 14.60^\circ$. Intensity data with $2\theta \leq 27.50^\circ$ were collected with the ω - 2θ scan technique at 2676 reflections. All reflections were corrected for Lorentz and polarization effects. Absorption

corrections were made with the *psi*-scan method. The crystal structure was resolved by direct methods using SHELXS-86 [23] and refined by full-matrix least-squares methods on F^2 using SHELXL-93 [24]. All non-H atoms were refined anisotropically. Hydrogen atoms were allowed as riding atoms with isotropic displacement parameters related to the non-H atoms on which they were riding.

Table 2. Crystal and experimental data for compound 4

Formula	C ₁₁ H ₁₀ N ₆ OS
Formula weight	274.31
Crystal system	monoclinic
Space group	$P2_1/c$
Unit-cell dimensions (Å)	$a = 7.2926(15)$ $b = 14.456(2)$ $c = 11.436(2)$ $\beta = 105.30(2)^\circ$
Unit-cell volume, V (Å ³)	1162.9(4)
Formula per unit cell, Z	4
D_{calcd} (g/cm ³)	1.567
Absorption coefficient, μ (mm ⁻¹)	0.28
$F(000)$	568
Crystal size (mm)	0.50 × 0.25 × 0.20
Index ranges	$-9 \leq h \leq 9$ $0 \leq k \leq 18$ $0 \leq l \leq 14$
Max. and min. transmission	0.9769 and 0.8844
Independent reflections	2676 ($R_{\text{int}} = 0.0000$)
Reflections/restraints/parameters	2676 / 0 / 173
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0363$, $wR_2 = 0.1041$
R indices (all data)	$R_1 = 0.0482$, $wR_2 = 0.1108$
Goodness-of-fit on F^2	1.062
Max. shift/error	-0.001
Largest difference peak and hole (e/Å ³)	0.377 and -0.304

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Sample availability: Samples of the title compound may be obtained from the authors.