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

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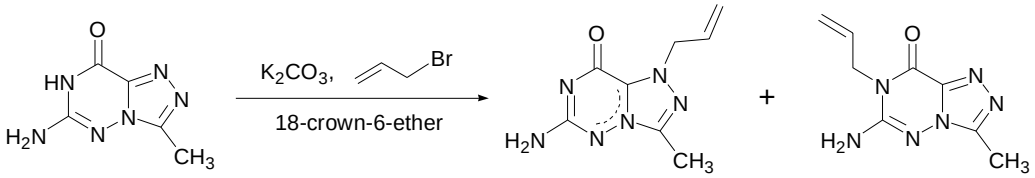
Abstract: 1-Allyl- (**2**) and 7-allyl-6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**3**) were obtained *via* the 18-crown-6-ether catalyzed room temperature reaction of 6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**1**) with potassium carbonate and allyl bromide in dry acetone. The structures of these two derivatives were verified by 2D-NMR measurements, including gHSQC and gHMBC measurements. The minor compound **2** may possess aromatic character. A single crystal X-ray diffraction experiment indicated that the major compound **3** crystallizes from dimethyl sulfoxide in the monoclinic space group $P2_1/n$ and its molecular structure includes an attached dimethyl sulfoxide molecule, resulting in the molecular formula $C_{10}H_{16}N_6O_2S$. Molecular structures of **3** are linked by extensive intermolecular N-H···N hydrogen bonding [graph set $C_1^1(7)$]. Each molecule is attached to the dimethyl sulfoxide oxygen *via* N-H···O intermolecular hydrogen bonding. 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; aromatic molecule; X-ray crystal structure; hydrogen bonds.

Introduction

Many aza/deaza analogues of purine have been found to display interesting biological activities. In the last decade numerous fused 1,2,4-triazines and fused 1,2,4-triazoloes have been synthesized and screened *in vitro/vivo*, thus revealing their varied biochemical, biological, pharmacological or cellular activities [1-19]. Recently, we have explored a ring cyclization mechanism [20,21] in connection with the preparation of the tautomeric heterobicyclic 6-amino-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (4,8-diaza-9-deazaguanine), the isosteric isomer of guanine and additionally we have proven by X-ray crystallographic analysis [22,23] that the predominant tautomeric structure of the former is the 7*H*-tautomer. To our knowledge, no report describing *N*-substituted derivatives of the tautomeric structure of 6-amino-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one has appeared to date. In continuation of our studies on the synthesis of derivatives and the tautomeric structures of the 6-amino-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one moiety, we report in this paper the synthesis and characterization of some *N*-allylated derivatives of 6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**1**), viz., 1-allyl-6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**2**) and 7-allyl-6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**3**) as potential bioactive molecules (Scheme 1). The molecular structures of **2** and **3** have been confirmed by spectral analysis, mainly their 2D-NMR. In addition, the single X-ray crystal structural analysis of molecule **3** is also reported, which supports the conclusions reached from the interpretation of the 2D-NMR spectral data.

Scheme 1



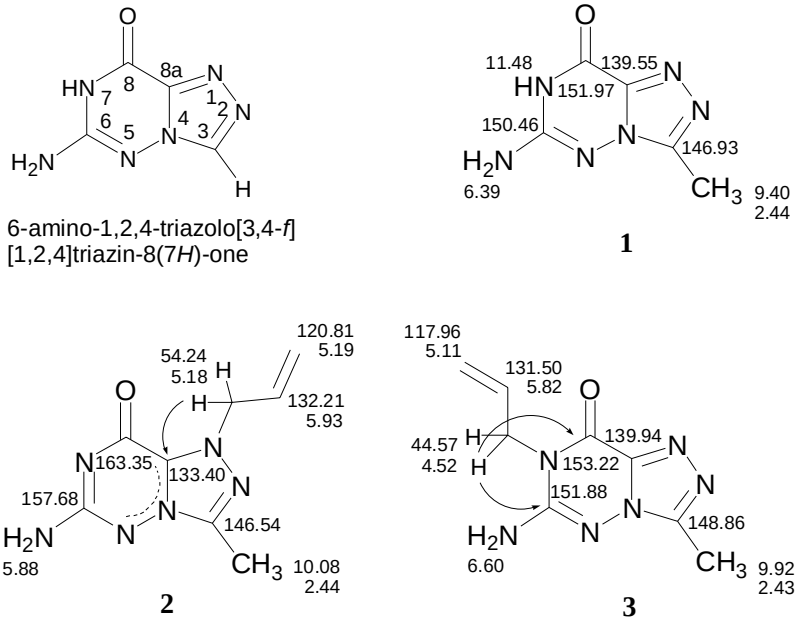
1 **2** **3**

Results and Discussion

Compound **1** was reacted with potassium carbonate and allyl bromide in dry acetone at room temperature for 16 h, under 18-crown-6-ether catalysis, to afford a 1:3 ratio of a minor product **2** (R_f = 0.59) and a major product **3** (R_f = 0.41) in 36% total yield. The structures of **1**, **2** and **3** were completely assigned by ^{1}H- and ^{13}C-NMR spectroscopy. The presence of an allyl group and eight carbon signals were observed in both compounds **2** and **3**. A detailed 2D-NMR study, including gHSQC and gHMBC measurements was necessary to confirm the allylation sites of **2** and **3**. The gHSQC ^{1}H-^{13}C experiments allowed segregation of the chemical shifts of proton or carbon for the 3-methyl, C-3 or allyl groups in **1**, **2** and **3**. The long-range gHMBC ^{1}H-^{13}C correlations showed the attachment of the allyl group on N-1 for structure **2**, since the methylene protons (δ_H 5.18 ppm) of this group show a ^3J (H,C) coupling to the C-8a carbon atom (δ_C 133.40 ppm). On the other hand, the fact that the methylene protons (δ_H 4.52 ppm) of the allyl group have a ^3J (H,C) coupling to both the C-6 (δ_C 151.88 ppm) and C-8 (δ_C 153.22 ppm) carbon atoms proved the attachment of the allyl group on N-7 for structure **3**.

Scheme 2 presents the numbering system of the 6-amino-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one moiety and complete assignment of ^{1}H- and ^{13}C-NMR signals for **1**, **2** and **3**, together with the corresponding long-range ^{1}H-^{13}C correlations. The δ values of ^{1}H- and ^{13}C-NMR of this moiety were similar in **1** and **3**. On the other hand, there were differences in the δ values of the ^{1}H- and ^{13}C-NMR spectra between the *N*-1-allyl **2** and *N*-7-allyl **3**; namely, the upfield shifts for 6-NH_2 group and C-8a between **2** and **3** were +0.72 and +6.54 ppm, respectively. Meanwhile, the δ values of C-6 and C-8 of **2** showed significant downfield shifts of -5.8 and -10.13 ppm, respectively, as compared to **3**. Similarly, the δ values of the methylene on the allyl group of **2** showed significant downfield shifts of -0.64 and -9.67 ppm, respectively, as compared to **3**. Taken together, molecule **2** revealed obvious differences in the NMR chemical shifts of C-6, C-8, C-8a, and the methylene on the allyl group, as compared to molecules **1** and **3**. This evidence suggests that **2** may be an aromatic molecule.

Scheme 2



The structure of **3** was unambiguously confirmed by X-ray crystallography of its adduct with dimethyl sulfoxide (DMSO), revealing the structural framework to be the 7-allyl-6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one connected with the oxygen of DMSO *via* N-H···O intermolecular hydrogen bonding (Figure 1). Obviously, the allyl group is located at N(5) (i.e., N-7), which is compatible with the tautomeric 7-H proton located at N-7 in the compounds 6-amino-3-ethyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one and 6-amino-3-benzylmercapto-1,2,4-triazolo[3,4-*f*]-[1,2,4]-triazin-8(7*H*)-one, as previously reported by us [22,23]. The mean plane of the 1,2,4-triazolo[3,4-*f*][1,2,4]triazine ring forms a dihedral angle of 89.14° with the N(5)-allyl group (N(5)-C(5)-C(6)-C(7)).

The molecular packing is shown in Figure 2. In the molecular structure of **3** the short bonds 1.306(3) Å (N(4)-C(4)), 1.316(3) Å (N(1)-C(2)) and 1.319(3) Å (N(2)-C(1)) have an appreciable double-bond character. Notably, the bond length 1.328(3) Å between C(4)-N(6) is shorter than 1.355 Å of C*ar*-NH_2 (Nsp^2: planar) [24].

Figure 1. ORTEP drawing and atom labelling scheme of the compound **3** (attached to DMSO) with thermal ellipsoids drawn at the 30% probability level.

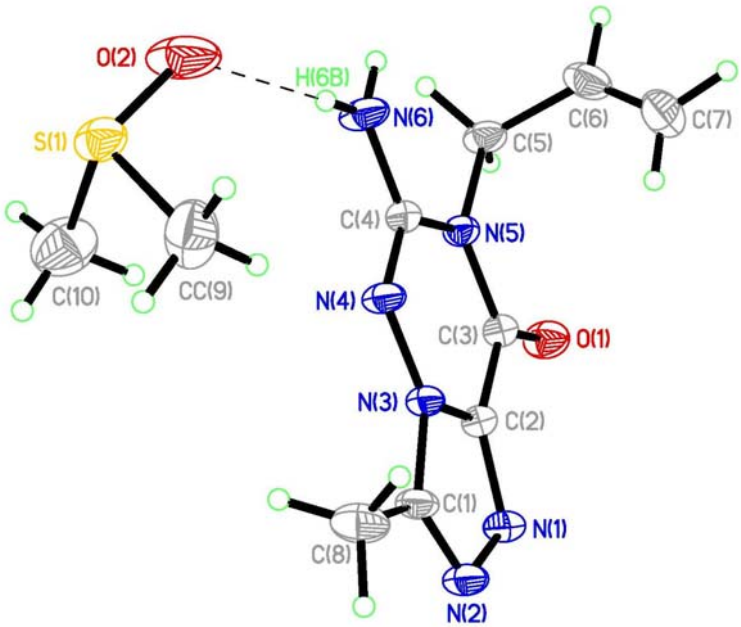
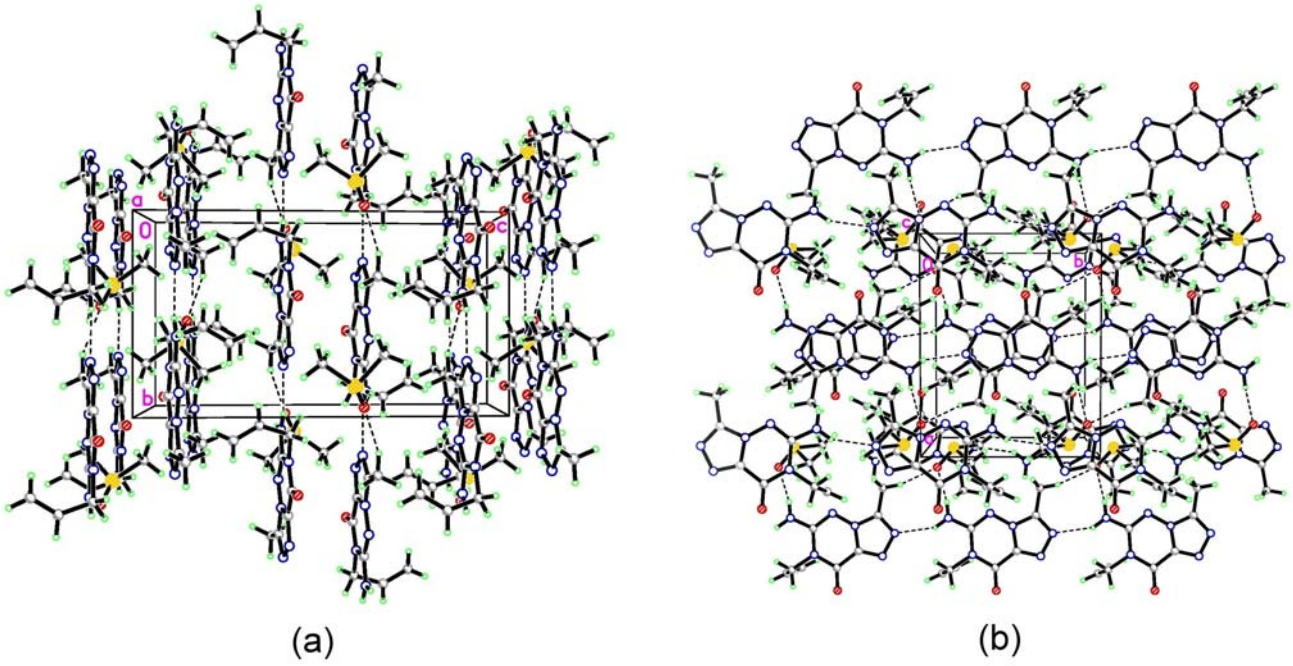


Figure 2. A perspective drawing of the packing arrangement of molecule **3**, showing (a) the molecules' direction along the *a*-view and (b) *c*-view with π-π stacking interactions. Dashed lines are intermolecular N−H···O hydrogen bonds.



Meanwhile, the 117.78°(19) value of the N(4)-C(4)-N(6) angle, close to 120°, confirms the sp^2 hybridization of the nitrogen atom, which implies 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 C(3)-O(1) bond length (1.214(3) Å) is shorter than the 1.240 Å bond length of Csp^2=O(1) in δ-lactams [24]. This may be attributed to the electron abstraction by the π-deficient heterobicyclic ring. In the structure of the

DMSO moiety the bond lengths of 1.771 (3) (S(1)-C(9)), 1.759(3) Å (S(1)-C(10)) and 1.482(2) Å (S(1)=O(2)) are all shorter than the 1.809 Å (S-C) and 1.497 Å (S=O) bond lengths in pure crystallized DMSO [24]. This is a result from the attraction of the intermolecular N-H···O hydrogen bonding in the crystal structure of **3**.

Analysis of the molecular packing in unit cell reveals that each molecular structure of **3** is linked by intermolecular hydrogen bonds and π-π stacking interactions (Figure 3 and Table 3). Each molecule is linked into $C_1^1(7)$ graph set association *via* N-H···N hydrogen bond interactions (Figure 3 notation [a] and [c]). Assignment of the H-bond descriptors is based on the graph-set theory [25]. The molecular graphic was obtained using the Mercury program (version 1.4, CCDC, Cambridge, UK). Meanwhile, each molecule links with the oxygen of DMSO *via* N-H···O hydrogen bonding ([b]). The structure is further stabilized by π-π stacking interactions (Figure 2: (b)), which results in the centroid···centroid distance (3.351 Å) being that between the layer of [1,2,4]triazolo[3,4-*f*][1,2,4]triazine ring.

Figure 3. A part of the crystal structure for molecule **3**, showing the molecules' direction along the *a*-view with x+90°. Broken lines indicate the intermolecular hydrogen bonding patterns. For notation and symmetry codes see Table 1.

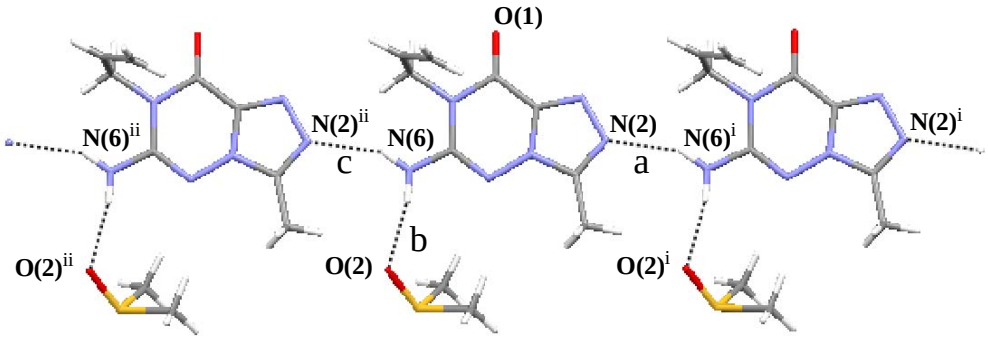


Table 1. Hydrogen bond geometry in compound **3.**

Notation	D-H···A	D-H (Å)	H···A (Å)	D···A (Å)	Length-VdW	D-H···A(°)
a	N(2)···H(6C)−N(6)^{i}	0.860	2.190	2.978	–0.122	152.27
b	N(6)−H(6B)···O(2)	0.860	2.033	2.848	–0.222	157.57
c	N(6)−H(6C)···N(2)^{ii}	0.860	2.190	2.978	–0.122	152.27

**Note.* Symmetry codes: (i) *x*, 1+*y*, *z*; (ii) *x*, –1+*y*, *z*.

Conclusions

In summary, we have reported the synthesis and molecular structure characterization of *N*-1-allyl **2** and *N*-7-allyl **3**. The 2D-NMR spectral analysis allowed complete assignments of various carbons of these molecules. Obviously different δ values in ^{1}H- and ^{13}C-NMR spectra between **2** and **3** were found. A single X-ray crystal structural analysis of **3** supported the evidence gathered from the NMR spectral interpretation.

Experimental Section

General

Melting points were measured on a YANACO micromelting point apparatus and were uncorrected. The Infrared spectra were recorded as KBr discs on a Perkin-Elmer FTIR 1650 instrument. The UV-VIS spectra were measured on a GBC Cintra 6 UV-Visible spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were obtained in dimethyl sulfoxide-d_6 (DMSO-d_6) on a Varian Mercury-plus 400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane (TMS) as an internal standard. For the assignments of signals, standard and long-range ^{1}H-^{13}C heteronuclear chemical shift correlation 2D-NMR experiments (gHSQC and gHMBC) were used. Thin layer chromatography (tlc) analyses were performed on silica gel plates (Merck 60 F_{254}, 0.2 mm thickness), and the components were detected by UV light (254 nm). Mass spectra were obtained on a Quattro VG-5022 spectrometer with an ionization potential of 70 eV. Elemental analyses were performed on a Heraeus CHN-O-Rapid elemental analyzer. All the solvents used were dried and distilled under argon prior to use.

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

Compound **1** was prepared as described by Lovelette [26], m.p. >300°C (from water); IR (cm^{-1}), ν_{max}: 3340, 3185, 1729 (C=O), 1625(C=N), 1517, 1408, 1283, 1131; UV, λ_{max} nm (log ε): (0.1 *N* HCl) 213 (4.35); (H_2O) 208 (4.56), 220 (4.56); (0.1 *N* NaOH) 208 (4.25), 220 (4.39); ^{1}H-NMR, δ: 2.44 (s, 3H, CH_3); 6.39 (s, 2H, NH_2); 11.48 (br s, 1H, NH); ^{13}C-NMR, δ: 9.40 (CH_3), 139.55 (C-8a), 146.93 (C-3), 150.46 (C-6), 151.97 (C-8); MS, m/z (%): 166 (M^+, 35), 138 (3), 123 (5), 111 (8), 97 (6), 91 (4), 77 (5), 69 (24), 54 (32), 43 (100). Anal. calcd for $C_5H_6N_6O$: C, 36.15%; H, 3.64%; N, 50.58%. Found: C, 36.10%; H, 3.70%; N, 50.74%.

1-Allyl-6-amino-3-methyl-1,2,4-triazolo[3,4-f][1,2,4]triazin-8(7H)-one (**2**) *and 7-Allyl-6-amino-3-methyl-1,2,4-triazolo[3,4-f][1,2,4]triazin-8(7H)-one* (**3**)

A solution of **1** (0.83 g, 5 mmol) in dry acetone (30 mL) was mixed with anhydrous potassium carbonate (0.69 g, 5 mmol) and a catalytic amount of 18-crown-6-ether (0.13 g, 0.5 mmol). Then allyl bromide (0.60 g, 5 mmol) was added and the mixture stirred at room temperature for 16 h. The solvent was evaporated to afford a crude product which was then applied to a silica gel (230-400 mesh) column. The column was eluted with a mixture of chloroform and methanol (50:1) and the appropriate fractions were combined and evaporated.

The R_f value of the minor adduct was 0.59 (chloroform- methanol = 5:1). The residue thus obtained was recrystallized from ethanol to give **2** (0.09 g, 9%) as bright white crystals, m.p. 278-279°C; IR (cm^{-1}), ν_{max}: 3384, 3321, 3141, 1706 (C=O), 1657 (C=N), 1591, 1493, 1425, 1315, 1267, 1098, 969, 919; UV, λ_{max} nm (log ε): (0.1 *N* HCl) 217 (4.41); (H_2O) 224 (4.66); (0.1 *N* NaOH) 218 (4.07); ^{1}H-NMR, δ: 2.44 (3H, CH_3), 5.18 (2H, CH_2), 5.19 (2H, CH=CH_2), 5.93 (1H, C*H*=CH_2), 5.88 (2H, 3-NH_2); ^{13}C-NMR, δ: 10.08 (CH_3), 54.24 (CH_2), 120.81 (CH=*C*H_2), 132.21 (*C*H=CH_2), 133.40 (C-8a), 146.54 (C-3), 157.68 (C-6), 163.35 (C-8); MS, m/z (%): 206 (M^+, 20), 165 (21), 164 (100), 111 (3), 84 (2), 69 (6), 54 (4), 42 (10); Anal. calcd for $C_{10}H_{10}N_4O$: C, 46.60%; H, 4.89%; N, 40.76%. Found: C, 46.72%; H, 4.86%; N, 40.65%.

The R_f value for the second (major) product was 0.41 (chloroform-methanol = 5:1). The residue thus obtained was recrystallized from ethanol to give **3** (0.28 g, 27%) as bright white crystals, m.p. 260-261°C; IR (cm^{-1}), ν_{max}: 3383, 3321, 3141, 1706 (C=O), 1658 (C=N), 1591, 1493, 1426, 1315, 1267, 1104, 967, 920; UV, λ_{max} nm (log ε): (0.1 *N* HCl) 208 (4.66), 213 (4.66), 218 (4.66); (H_2O) 220 (4.41); (0.1 *N* NaOH) 218 (4.10); ^{1}H-NMR, δ: 2.43 (3H, CH_3), 4.52 (2H, CH_2), 5.11 (2H, CH=C*H*$_2$), 5.82 (1H, C*H*=CH_2), 6.60 (2H, 3-NH_2); ^{13}C-NMR, δ: 9.92 (CH_3), 44.57 (CH_2), 117.96 (CH=*C*H_2), 131.50 (*C*H=CH_2), 139.94 (C-8a), 148.86 (C-3), 151.88 (C-6), 153.22 (C-8); MS, m/z (%): 206 (M^+, 100), 191 (71), 177 (8), 165 (17), 164 (35), 151 (10), 135 (13), 123 (6), 111 (6), 96 (5), 84 (7), 69 (10), 54 (15); Anal. calcd for $C_{10}H_{10}N_4O$: C, 46.60%; H, 4.89%; N%, 40.76. Found: C, 46.60%; H, 4.93%; N, 40.70%.

Table 2. Crystal and experimental data for compound **3.**

Formula	$C_{10}H_{16}N_6O_2S$
Formula weight	284.35
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit-cell dimensions (Å)	a = 10.4850(6)
	b = 8.4409(5)
	c = 15.5152(9)
	β = 95.963(1)°
Unit-cell volume, V (Å^3)	1365.71(14)
Formula per unit cell, Z	4
D_{calcd} (g/cm^3)	1.383
Absorption coefficient, μ (mm^{-1})	0.246
F(000)	600
Crystal size (mm)	0.36 × 0.25 × 0.08
Index ranges	$-13 \le h \le 13$
	$-10 \le k \le 10$
	$-20 \le l \le 20$
Max. and min. transmission	0.9806 and 0.9167
Independent reflections	3133 (R_{int} = 0.0480)
Reflections/restraints/parameters	3133 /0 /175
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0590, wR_2 = 0.1371
R indices (all data)	R_1 = 0.0736, wR_2 = 0.1454
Goodness-of-fit on F^2	1.078
Max. shift/error	0.000

X-ray techniques

X-ray quality crystals of compound **3** were obtained by crystallization from dimethyl sulfoxide at room temperature. A summary of the crystallographic data and details of the structure refinements is listed in Table 2. The data was collected on a BRUKER SMART ApexCCD diffractometer with a graphite-monochromated Mo*Kα* radiation (λ = 0.71073 Å) at 295(2) K. The crystal structure has been

deposited at the Cambridge Crystallographic Data Centre [27]. A total of 13191 reflections and 3133 independent reflections (R_{int} = 0.0480) were collected within the range of 2.24 <θ< 27.50° by using the ω scan technique, of which 2535 observed reflections with $I > 2\sigma(I)$ were used in the structural analysis. The crystal structure was solved by direct methods using SHELXS-97 [28] and refined by full-matrix least-squares methods on F^2 using SHELXL-97 [29]. All non-H atoms were refined anisotropically. The hydrogen atoms were placed geometrically and refined as riding. The final cycle of full-matrix least-squares refinement gave R_1 = 0.0416, wR_2 = 0.1142 ($w = 1/[\sigma^2(F_o^2) + (0.0584P)^2 + 0.7097P]$, where $P = (F_o^2 + 2F_c^2)/3$). S = 1.078 and $(\Delta/\sigma)_{max}$ = 0.000. The maximum peak on the final difference Fourier map is 0.321 and the minimum peak −0.319 eÅ^{-3}.

Acknowledgements

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Sample Availability: Samples of the compounds mentioned are available from the authors.