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(7H)-one

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Received: 31 May 2006; in revised form: 17 June 2006 / Accepted: 19 June 2006 / Published: 22 June 2006

Abstract: 1-Allyl- (2) and 7-allyl-6-amino-3-methyl-1,2,4-triazolo[3,4-f][1,2,4]triazin-8(7H)-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(7H)-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_{6}O_{2}S. 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(7H)-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 7H-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(7H)-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(7H)-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(7H)-one (1), viz., 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) 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

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 ($\delta_H 5.18$ ppm) of this group show a $^3J(H,C)$ coupling to the C-8a carbon atom ($\delta_C 133.40$ ppm). On the other hand, the fact that the methylene protons ($\delta_H 4.52$ ppm) of the allyl group have a $^3J(H,C)$ coupling to both the C-6 ($\delta_C 151.88$ ppm) and C-8 ($\delta_C 153.22$ 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 \(\delta\) 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 \(\delta\) 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 \(\delta\) 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 \(\delta\) 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.

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 Car-NH\(_2\) (N\(sp^2\): 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 $\pi$-$\pi$ 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 $\delta$-lactams [24]. This may be attributed to the electron abstraction by the $\pi$-deficient heterobicyclic ring. In the structure of the
DMSO moiety the bond lengths of 1.771 (3) Å (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.

![Crystal Structure](image)

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

<table>
<thead>
<tr>
<th>Notation</th>
<th>D-H···A</th>
<th>D-H (Å)</th>
<th>H···A (Å)</th>
<th>D···A (Å)</th>
<th>Length-VdW</th>
<th>D-H···A(°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>N(2)···H(6C)···N(6)i</td>
<td>0.860</td>
<td>2.190</td>
<td>2.978</td>
<td>−0.122</td>
<td>152.27</td>
</tr>
<tr>
<td>b</td>
<td>N(6)···H(6B)···O(2)</td>
<td>0.860</td>
<td>2.033</td>
<td>2.848</td>
<td>−0.222</td>
<td>157.57</td>
</tr>
<tr>
<td>c</td>
<td>N(6)···H(6C)···N(2)ii</td>
<td>0.860</td>
<td>2.190</td>
<td>2.978</td>
<td>−0.122</td>
<td>152.27</td>
</tr>
</tbody>
</table>

*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 $\delta$ 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 ($\delta$) 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 ($g$HSQC and $g$HMBC) 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$^{-1}$), $\nu$ max: 3340, 3185, 1729 (C=O), 1625(C=N), 1517, 1408, 1283, 1131; UV, $\lambda$ max nm (log $\varepsilon$): (0.1 N HCl) 213 (4.35); (H$_2$O) 208 (4.56), 220 (4.56); (0.1 N NaOH) 208 (4.25), 220 (4.39); $^1$H-NMR, $\delta$: 2.44 (s, 3H, CH$_3$); 6.39 (s, 2H, NH$_2$); 11.48 (br s, 1H, NH); $^{13}$C-NMR, $\delta$: 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$_5$H$_6$N$_6$O: 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 (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$^{-1}$), $\nu$ max: 3384, 3321, 3141, 1706 (C=O), 1657 (C=N), 1591, 1493, 1425, 1315, 1267, 1098, 969, 919; UV, $\lambda$ max nm (log $\varepsilon$): (0.1 N HCl) 217 (4.41); (H$_2$O) 224 (4.66); (0.1 N NaOH) 218 (4.07); $^1$H-NMR, $\delta$: 2.44 (3H, CH$_3$), 5.18 (2H, CH$_2$), 5.19 (2H, CH=CH$_2$), 5.93 (1H, CH=CH$_2$), 5.88 (2H, 3-NH$_2$); $^{13}$C-NMR, $\delta$: 10.08 (CH$_3$), 54.24 (CH$_2$), 120.81 (CH=CH$_2$), 132.21 (CH=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$_4$O: 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$^{-1}$), $\nu_{\text{max}}$: 3383, 3321, 3141, 1706 (C=O), 1658 (C=N), 1591, 1493, 1426, 1315, 1267, 1104, 967, 920; UV, $\lambda_{\text{max}}$ nm (log $\varepsilon$): (0.1 N HCl) 208 (4.66), 213 (4.66), 218 (4.66); (H$_2$O) 220 (4.41); (0.1 N NaOH) 218 (4.10); $^1$H-NMR, $\delta$: 2.43 (3H, CH$_3$), 4.52 (2H, CH$_2$), 5.11 (2H, CH=CH$_2$), 5.82 (1H, CH=CH$_2$), 6.60 (2H, 3-NH$_2$); $^{13}$C-NMR, $\delta$: 9.92 (CH$_3$), 44.57 (CH$_2$), 117.96 (CH=CH$_2$), 131.50 (CH=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$_4$O: 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.

<table>
<thead>
<tr>
<th>Formula</th>
<th>C$<em>{10}$H$</em>{16}$N$_6$O$_2$S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula weight</td>
<td>284.35</td>
</tr>
<tr>
<td>Crystal system</td>
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<tr>
<td>Space group</td>
<td>$P2_1/n$</td>
</tr>
<tr>
<td>Unit-cell dimensions (Å)</td>
<td>$a = 10.4850(6)$</td>
</tr>
<tr>
<td></td>
<td>$b = 8.4409(5)$</td>
</tr>
<tr>
<td></td>
<td>$c = 15.5152(9)$</td>
</tr>
<tr>
<td></td>
<td>$\beta = 95.963(1)^\circ$</td>
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<tr>
<td>Unit-cell volume, $V$ (Å$^3$)</td>
<td>1365.71(14)</td>
</tr>
<tr>
<td>Formula per unit cell, $Z$</td>
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<tr>
<td>$D_{\text{calcd}}$ (g/cm$^3$)</td>
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</tr>
<tr>
<td>Absorption coefficient, $\mu$ (mm$^{-1}$)</td>
<td>0.246</td>
</tr>
<tr>
<td>$F(000)$</td>
<td>600</td>
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<tr>
<td>Crystal size (mm)</td>
<td>$0.36 \times 0.25 \times 0.08$</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>$-10 \leq k \leq 10$</td>
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<tr>
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<td>$-20 \leq l \leq 20$</td>
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<tr>
<td>Max. and min. transmission</td>
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<tr>
<td>Independent reflections</td>
<td>3133 ($R_{\text{int}} = 0.0480$)</td>
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<td>Final $R$ indices [$I &gt; 2\sigma(I)$]</td>
<td>$R_1 = 0.0590$, $wR_2 = 0.1371$</td>
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<tr>
<td>$R$ indices (all data)</td>
<td>$R_1 = 0.0736$, $wR_2 = 0.1454$</td>
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<td>Goodness-of-fit on $F^2$</td>
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<td>Max. shift/error</td>
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</table>

**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 MoK$\lambda$ radiation ($\lambda = 0.71073$ 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 \( R_{\text{int}} = 0.0480 \) were collected within the range of \( 2.24 < \theta < 27.50^\circ \) by using the \( \omega \) 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 \( R_1 = 0.0416, \ wR_2 = 0.1142 \) \( w = 1/\left[\sigma^2(F^2_{o}) + (0.0584P)^2 + 0.7097P\right] \), where \( P = (F^2_{o} + 2F^2_{c})/3 \). \( S = 1.078 \) and \( (\Delta/\sigma)_{\text{max}} = 0.000 \). The maximum peak on the final difference Fourier map is 0.321 and the minimum peak \(-0.319 \text{ eÅ}^{-3}\).

Acknowledgements

The authors would like to thank the National Science Council, Republic of China, for support under grant NSC 90-2113-M-037-015.

References and Notes

27. CCDC 608157 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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