Synthesis and Crystal Structure of Novel Schiff Bases Derived from 3-(2-Ethoxyphenyl)-4-Amino-5-Mercapto-4*H*-1,2,4-Triazole

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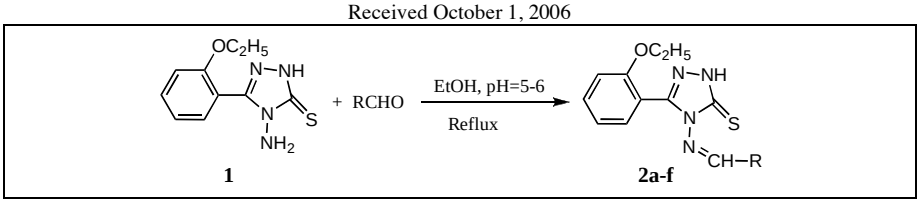

A series of novel 4-(arylmethylidene)amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazoles (**2a-f**) were easily synthesized in high yields by means of the reactions of 3-(2-ethoxyphenyl)-4-amino-5-mercapto-4*H*-1,2,4-triazole (**1**) with various aromatic aldehydes. The compound, 4-(4-methylbenzylidene)-amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazole was investigated with X-ray crystallography.

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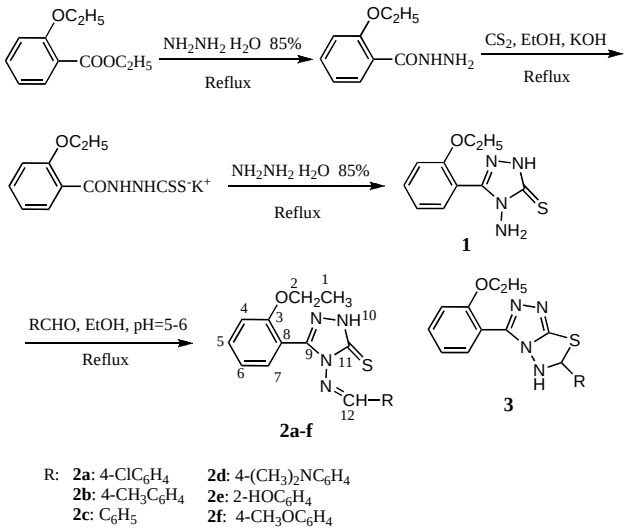
INTRODUCTION

1,2,4-triazoles and their derivatives were reported to possess significant antibacterial, antifungal, antiviral, anticancer and antihelmintic activities [1-8]. Schiff bases and their complexes are becoming increasingly important as biochemical, analytical and antimicrobial reagents [9], and have been amongst the most widely studied coordination compounds in recent years. Further, many Schiff bases of 1,2,4-triazoles were found to possess potent activities such as herbicidal, pesticidal, plantgrowth regulating [10,11]. In particular, Schiff bases derived from triazoles are more and more interesting because of their broad spectra of biological activities. Our researches have been devoted for several years to the synthesis of a series of novel derivatives derived from 1,2,4-triazoles compounds [12-17]. However, we noticed that the crystal structure of this heterocyclic system was not reported in literature up to now. Therefore, it is planned to investigate a new system, which combines these biological components together to obtain new biological activities. Considering that ethyl 2-ethoxylbenzoate may play a special role in the body, we have synthesized several novel 4-(arylmethylidene) amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4- triazoles (**2a-f**), which may improve their transportation and absorption in biological systems. The structures of all products have been characterized by elemental analysis, ir, ^{1}H nmr, and ^{13}C nmr. The synthetic route to the compounds is shown in Scheme 1. The compound, 4-(4-methylbenzylidene)amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazole (**2b**) was investigated with X-ray crystallography.

Scheme 1

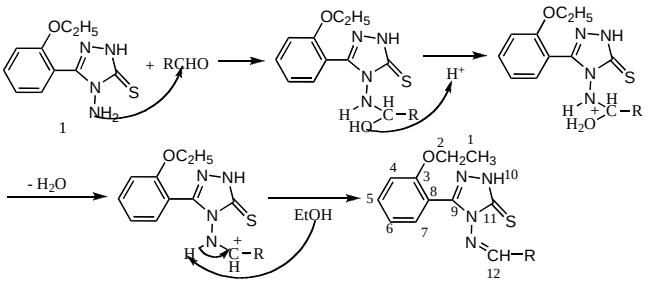


RESULTS AND DISCUSSION

In the beginning, we applied a previously reported procedure [18] and treated the triazole **1** with the various aromatic aldehydes maintaining the pH values during the reaction at 5–6 in order to attempt to get the ring closed derivatives **3**. As reported previously [18], the acidity of the reaction medium is crucial, and if it is too high or too low the ring closed derivatives **3** will not be obtained. However, we ran this reaction under the above mentioned conditions, we could only obtain the open chain hydrazones **2a-f** by way of recrystallization. The reason may be that the acidity of the reaction medium (pH=5-6) is too low for the dehydration necessary to obtain the ring-closed derivatives **3**. The mechanism is presented in Scheme 2.

IR absorption bands of **2a-f** at 3431-3447 cm^{-1} are assigned to its NH group. The $\nu_{C=N}$ absorption bands of compounds **2a-f** are in the region of 1602-1620 cm^{-1} and

Scheme 2



the $\nu_{C=S}$ absorption bands are in the region of 1039-1264 cm^{-1}.

In the ^1H nmr and ^{13}C nmr spectra we observe the peak of the $N=C_{12}$-H proton at 9.79–9.10 ppm and the corresponding carbon at about 160 ppm, which show that the synthesized products are the above mentioned open chain structure. A downfield signal appearing at 14.16-13.97 ppm is attributed to the $N\text{-}H_{10}$ proton. A triplet at 1.1 ppm in the ^1H nmr spectra and the corresponding carbon at about 14 ppm ^{13}C nmr spectra are attributable to the $-C^1H_3$ group. A quartet at 3.9 ppm in the ^1H nmr spectra and the corresponding carbon at about 63 ppm ^{13}C nmr spectra are attributable to the $-OC^2H_2$- group. The remaining protons resonated as multiplets in the aromatic region δ 7.0-7.8 ppm.

The crystal data and summary of data collection and structure refinement of **2b** are given in Table 1. Selected bond lengths and angles are given in Table 2. The geometric calculations were performed using the program SHELXL-97.

In the crystal compound **2b**, the bond lengths indicate a degree of delocalization around the system which is composed by the triazole ring and –N=CH- group, with the two C=N bonds ranging from 1.276(3) to 1.301(3) Å and the two N-N bonds ranging from 1.377(3) to 1.408(3) Å. The crystal packing is stabilized by N—H···O and N—H···S intra- and intermolecular hydrogen-bonding interactions. The structure of the compound **2b** is shown in Figure 1.

EXPERIMENTAL

All melting points were determined on an XT-4A apparatus and are uncorrected. The nmr spectra were measured on a Bruker Advance 300 spectrometer in DMSO-d_6 solutions using TMS as internal reference. Elemental analyses were carried out with an EA 1112 elemental analyzer. The crystal structure was measured on Bruker APEX area-detector diffractometer. All the reagents used were AR grade.

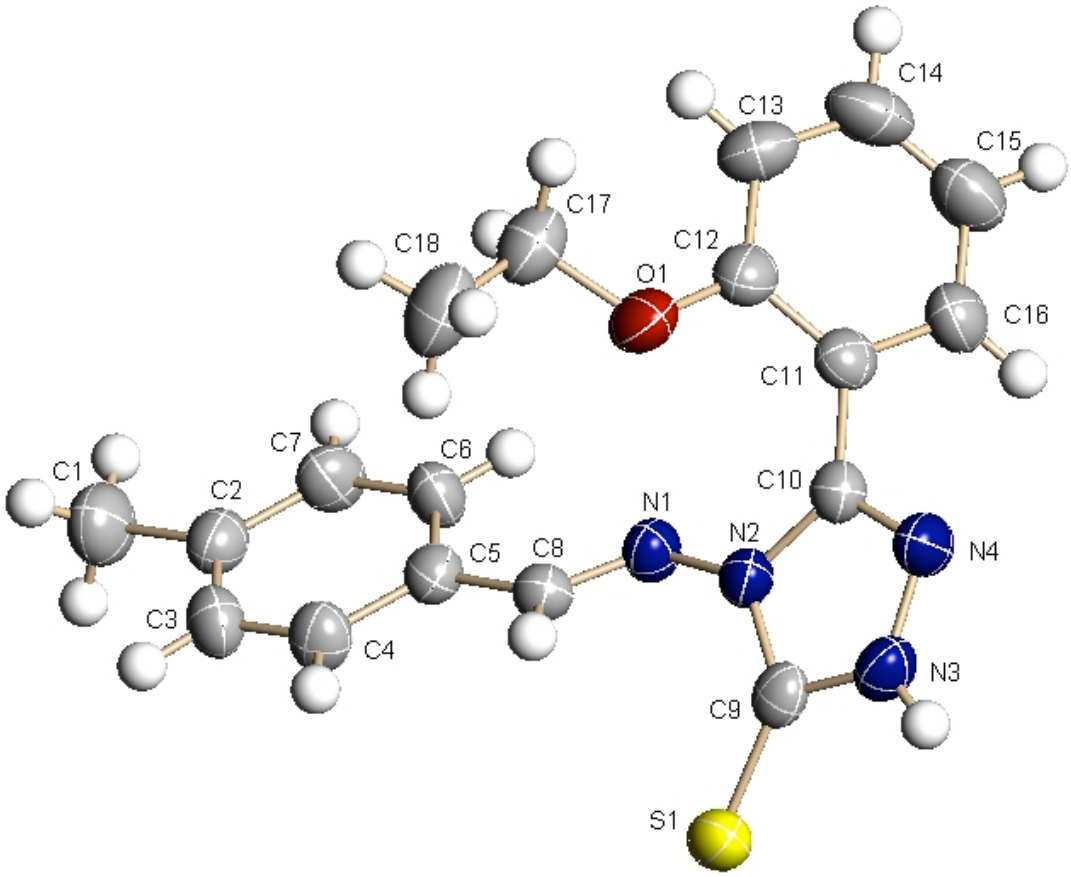


Figure 1. The molecular structure of **2b**, with the atom-numbering, showing displacement ellipsoids at the 30% probability level.

Table 1

Crystal data and summary of data collection and structure refinement

Compound	$C_{18}H_{18}N_4OS$
Color	Colorless
Formula weight	338.43
Crystal system, space group	Orthorhombic, P 2_1 2_1 2_1
Temperature,℃	25(298K)
Cell constants	
a (Å)	13.881(9)
b (Å)	8.379(5)
c (Å)	15.220(10)
α (°)	90
β (°)	90
γ (°)	90
Volume ($Å^3$)	1770.2(19)
Formula units	4
Calculated density (Mg/m^3)	1.270
F(000)	712
Absorption coefficient, mm^{-1}	0.195
Limiting indices	$-16 \le h \le 16$; $-9 \le k \le 9$; $-10 \le l \le 18$
Reflections collected / unique	9178 / 3129 (R(int) = 0.0235)
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9466 and 0.9193
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3129 / 0 / 219
Goodness-of-fit on F^2	1.166
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0448$, $wR_2 = 0.1054$
R indices (all data)	$R_1 = 0.0466$, $wR_2 = 0.1064$
Absolute structure parameter	0.04(10)
Largest diff. peak and hole (e $Å^{-3}$)	0.214 and -0.175

The appropriate aromatic aldehyde (1.1 mmol) was added to a solution of 4-amino-5-(4-ethoxyphenyl)-3-mercapto-1,2,4-triazole (**1**, 236 mg, 1 mmol) in ethanol (10 ml). The pH values was then adjusted to 5–6 with diluted HCl and the mixture was heated at 90 °C for 5 h, allowed to stand overnight and the precipitate was collected by filtration, washed with a 5% $NaHCO_3$ solution (30 ml) and water and air-dried. The crude product was then recrystallized from ethanol and distilled water (8:2, volume) to yield pure **2a-f**.

The purified product, 4-(4-methylbenzylidene)amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazole (**2b**) was dissolved in 95% ethanol and kept at room temperature for 4 days and single crystals of **2b** were formed.

4-(4-Chlorobenzylidene)amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazole(2a). yield 75%; mp 204-205°; ir(cm^{-1}): 3431 (NH), 3042 (ArH), 2981 (CH_3), 2925 (CH_2), 1620 (C=N), 1578, 1536, 1487 (Ar skeleton), 1123 (C=S); ^{1}H nmr (300 MHz, $CDCl_3$, 25°, TMS) δ (ppm): 14.16 (s, 1H, NH-C=S), 9.73 (s, 1H, N=CH), 7.80-7.05 (m, 8H, Ar-H), 3.93 (q, 2H, *J* = 6.9 Hz, OCH_2), 1.08 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ (ppm): 163.66, 161.74, 160.47, 156.72, 148.33, 132.58, 131.33, 129.98, 129.33, 129.04, 120.30, 114.54, 112.34, 63.52, 14.23; Elemental anal. Calc. (%) for $C_{17}H_{15}ClN_4OS$(358.9): C 56.90, H 4.21, N 15.61; Found: C 56.96, H 4.11, N 15.54.

5-(2-Ethoxyphenyl)-4-(4-methylbenzylidene)amino-3-mercapto-4*H*-1,2,4-triazole(2b). yield 85%; mp 196-197°; ir(cm^{-1}): 3447 (NH), 3107 (ArH), 2982 (CH_3), 2926 (CH_2), 1605 (C=N), 1589, 1506, 1456 (Ar skeleton), 1202 (C=S); ^{1}H nmr (300 MHz, $CDCl_3$, 25°, TMS) δ (ppm): 14.13 (s, 1H, NH-C=S), 9.54 (s, 1H, N=CH), 7.67-7.05 (m, 8H, Ar-H), 3.91 (q, 2H, *J* = 6.9 Hz, OCH_2), 2.36 (s, 3H, Ar-CH_3), 1.08 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ (ppm): 163.44, 161.77, 156.73, 148.24, 142.93, 132.71, 131.31, 129.70, 129.32, 128.39, 120.27, 114.68, 112.31, 63.50, 21.17, 14.23; Elemental anal. Calc. (%) for $C_{18}H_{18}N_4OS$(338.4): C 63.88, H 5.36, N 16.56; Found: C 63.79, H 5.25, N 16.46.

4-(Benzylidene)amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazole(2c). yield 86%; mp 202-203°; ir(cm^{-1}): 3445 (NH), 3091 (ArH), 2983 (CH_3), 2925 (CH_2), 1614 (C=N), 1599, 1506, 1460 (Ar skeleton), 1130 (C=S); ^{1}H nmr (300 MHz,

Table 2

Selected bond lengths (Å) and angles (°) for **5b**

S(1)-C(9) 1.693(3)	O(1)-C(12) 1.367(3)	O(1)-C(17) 1.434(3)
N(1)-C(8) 1.276(3)	N(1)-N(2) 1.408(3)	N(2)-C(9) 1.381(3)
N(2)-C(10) 1.384(3)	N(3)-C(9) 1.338(3)	N(3)-N(4) 1.377(3)
N(4)-C(10) 1.301(3)	C(1)-C(2) 1.510(4)	C(2)-C(3) 1.392(4)
C(2)-C(7) 1.396(4)	C(3)-C(4) 1.383(4)	C(4)-C(5) 1.395(3)
C(5)-C(6) 1.398(3)	C(5)-C(8) 1.467(3)	C(6)-C(7) 1.374(4)
C(10)-C(11) 1.485(4)	C(11)-C(12) 1.395(4)	C(11)-C(16) 1.398(4)
C(12)-C(13) 1.401(4)	C(13)-C(14) 1.381(5)	C(14)-C(15) 1 .370(5)
C(15)-C(16) 1.383(4)	C(17)-C(18) 1.479(5)	
C(12)-O(1)-C(17) 118.8(2)	C(8)-N(1)-N(2) 114.13(19)	C(9)-N(2)-C(10) 108.08(19)
C(9)-N(2)-N(1) 127.92(19)	C(10)-N(2)-N(1) 122.79(18)	C(9)-N(3)-N(4) 114.24(19)
C(10)-N(4)-N(3) 103.9(2)	C(3)-C(2)-C(7) 117.5(2)	C(3)-C(2)-C(1) 120.6(2)
C(7)-C(2)-C(1) 121.9(2)	C(4)-C(3)-C(2) 121.1(2)	C(3)-C(4)-C(5) 120.9(2)
C(4)-C(5)-C(6) 118.3(2)	C(4)-C(5)-C(8) 119.2(2)	C(6)-C(5)-C(8) 122.5(2)
C(7)-C(6)-C(5) 120.3(2)	C(6)-C(7)-C(2) 121.9(2)	N(1)-C(8)-C(5) 121.8(2)

3-(2-Ethoxyphenyl)-4-amino-5-mercapto-4*H*-1,2,4-triazole (1). The key intermediate (**1**) was prepared from acid hydrazide, whose starting material was 2-ethoxybenzoic acid, following the method of reference [19]. yield 63.2%, mp 153-154°, ^{1}H nmr (DMSO-d_6) δ (ppm): 13.81 (s, 1H, –NH-C=S), 7.55-7.02 (m, 4H, ArH), 5.39 (s, 2H, NH_2), 4.11 (q, 2H, *J*=6.9Hz, OCH_2),1.27 (t, 3H, J=6.9Hz, CH3); 13C nmr (DMSO-d6) δ (ppm): 165.70, 157.09, 149.23, 132.46, 131.47, 120.32, 115.17, 112.64, 64.01, 14.48.

General Method for the Preparation of 4-(Aryl methylidene)amino-5-(2-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazoles (2a-f). Reaction of the triazole **1** and the appropriate aromatic aldehydes in absolute ethanol maintaining the pH values during the reaction at 5–6 afforded the Schiff bases **2a–f**.

$CDCl_3$, 25°, TMS) δ (ppm): 14.14 (s, 1H, NH-C=S), 9.67 (s, 1H, N=CH), 7.77-7.07 (m, 9H, Ar-H), 3.92 (q, 2H, *J* = 6.9 Hz, OCH_2), 1.08 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ (ppm): 165.20, 161.78, 156.75, 148.30, 132.73, 132.56, 132.03, 131.33, 129.09, 128.35, 120.28, 114.65, 112.34, 63.53, 14.22; Elemental anal. Calc. (%) for $C_{17}H_{16}N_4OS$(324.4): C 62.94, H 4.97, N 17.27; Found: C 62.86, H 4.81, N 17.13.

5-(4-Ethoxyphenyl)-4-(4-(*N*,*N*-dimethylamino)benzylidene)-amino-3-mercapto-4*H*-1,2,4-triazole(2d). yield 70%; mp 243-244°; ir(cm^{-1}): 3432 (NH), 3084 (ArH), 2980 (CH_3), 2919 (CH_2), 1612 (C=N), 1585, 1533, 1503 (Ar skeleton), 1175 (C=S); ^{1}H nmr (300 MHz, $CDCl_3$, 25°, TMS) δ (ppm): 13.97 (s, 1H, NH-C=S), 9.10 (s, 1H, N=CH), 7.57-6.72 (m, 8H, Ar-H), 3.91 (q, 2H, *J* = 6.9 Hz, OCH_2), 3.00 (s, 6H, $N(CH_3)_2$), 1.12 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ (ppm): 166.54, 161.82, 156.73, 153.02, 148.05, 132.53, 131.29, 130.15, 120.20, 118.58, 114.97, 112.30, 111.46, 63.48, 40.46, 14.25, 165.33; Elemental anal. Calc. (%) for $C_{19}H_{21}N_5OS$ (367.5): C 62.10, H 5.76, N 19.06; Found: C 61.91, H 5.69, N 18.95.

5-(4-Ethoxyphenyl)-4-(2-hydroxybenzylidene)amino-3-mercapto-4*H*-1,2,4-triazole (2e). yield 83%; mp 207-208°; ir(cm^{-1}): 3447 (NH), 3076 (ArH), 2983 (CH_3), 2926 (CH_2), 1611 (C=N), 1558, 1516, 1460 (Ar skeleton), 1204 (C=S); ^{1}H nmr (300 MHz, $CDCl_3$, 25°, TMS) δ (ppm): 14.10 (s, 1H, NH-C=S), 10.39 (s, 1H, OH), 9.79 (s, 1H, N=CH), 7.61-6.86 (m, 8H, Ar-H), 3.94 (q, 2H, *J* = 6.9 Hz, OCH_2), 1.13 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ (ppm): 162.80, 161.80, 158.35, 156.70, 148.14, 134.19, 132.75, 131.32, 127.71, 120.32, 119.54, 117.87, 116.57, 114.59, 112.29, 63.60, 14.12; Elemental anal. Calc. (%) for $C_{17}H_{16}N_4O_2S$ (340.4): C 59.98, H 4.74, N 16.46; Found: C 60.06, H 4.56, N 16.38.

5-(4-ethoxyphenyl)-4-(4-methoxybenzylidene)amino-3-mercapto-4*H*-1,2,4-triazole (2f). yield 76%; mp 200-201°; ir(cm^{-1}): 3445 (NH), 3091 (ArH), 2983 (CH_3), 2925 (CH_2), 1602 (C=N), 1566, 1506, 1457 (Ar skeleton), 1115 (C=S); ^{1}H nmr (300 MHz, $CDCl_3$, 25°, TMS) δ (ppm): 14.08 (s, 1H, NH-C=S), 9.42 (s, 1H, N=CH), 7.74-7.03 (m, 8H, Ar-H), 3.91 (q, 2H, *J* = 6.9 Hz, OCH_2), 3.82 (s, 3H, OCH_3), 1.09 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ (ppm): 165.53, 162.76, 161.75, 156.71, 148.16, 132.67, 131.31, 130.38, 124.42, 120.26, 114.72, 114.60, 112.31, 63.49, 55.45, 14.23; Elemental anal. Calc. (%) for $C_{18}H_{18}N_4O_2S$(354.4): C 61.00, H 5.12, N 15.81; Found: C 60.95, H 5.01, N 15.84.

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