One pot synthesis and reactions of novel 5-amino[1,3]thiazolo[3,2-b][1,2,4]triazoles


Chemistry Department, Faculty of Science, Assiut University
Assiut 71516, Egypt
E-mail: dr_Hassanahmed@yahoo.com

Abstract
5-Mercapto-3-phenyl-1,2,4-triazole 8 was reacted with a variety of cyano compounds containing active methylene group such as ethyl cyanoacetate, cyanoacetamide and malonitrile in boiling acetic acid in the presence of concentrated sulfuric acid, to give the corresponding 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxylate 10a. While on using cyanoacetamide or malonitrile the 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide 10b was obtained in one step reaction. Reaction of 10b with triethyl orthoformate, acetic anhydride, benzaldehyde, benzoyl chloride and/or carbon disulfide gave the corresponding 2-phenyl[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-d]pyrimidinones 15-18 in good yield. Upon treatment of 5-mercapto-3-phenyl-1,2,4-triazole 8 with chloroacetoneitrile and benzaldehyde in boiling acidified acetic acid afforded 6-benzylidene-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazol-5(6H)-one 19 rather than the isomeric product 6-benzylidene-3-phenyl[1,3]thiazolo[2,3-c][1,2,4]triazol-5(6H)-one 20 in one pot reaction. The mechanism of the reactions is under investigation and the structures of all new compounds were elucidated using IR, ¹H-NMR, ¹³C-NMR, mass spectral data and elemental analysis. The biological activity of selected compounds was investigated and summarized.

Keywords: Acidified acetic acid condition (AcOH/H⁺), α-hydrogen, nitriles, one pot reaction, thiazolotriazoles, triazolothiazolopyrimidinones

Introduction

The thiazole nucleus is present in various molecules having biological activity.¹-¹³ The 1,2,4-triazole moiety is present in antiarthritic and antipyretic compounds.¹⁴-¹⁹ Many thiazolo[3,2-b][1,2,4]triazoles have been investigated as antibacterials,²⁰,²¹ anticancer,²² anti-inflammatory,²₃-²⁵ antimicrobial²⁴ and analgesic²⁵ compounds. To the best of our knowledge the title compounds
have been synthesized by three main routes according to a literature survey. In the first route the triazole ring is built onto a thiazole ring via reaction of 2-imino-3-amino thiazoles with acids, anhydrides or phosgene immonium chloride, or cyclization of 2-acylamino-3-amino thiazolines. In the second route the thiazole ring is built onto a triazole ring via reaction of 3-mercapto-1,2,4-triazoles with α-haloketones followed by cyclization of the thiomethylketone intermediate using PPA, via reaction of 3-mercapto-1,2,4-triazoles with allyl bromide in the presence of aqueous sodium hydroxide solution, or in a one step reaction using the mercaptotriazole, chloroaetic acid and aromatic aldehydes. The third route involves chalcones reacting with bis(1-H-1,2,4-triazolyl)sulfoxide to form thiazolo[3,2-b][1,2,4]triazoles. The present study is part of our program aimed at developing easy routes for the synthesis of fused heterocyclic compounds starting with cyano compounds containing active methylene groups. Thus we applied our method for the synthesis of thiazolo[3,2-a]benzimidazoles, imidazo[2,1-b]thiazoles, 2-benzylthiazolo[3,2-b][1,2,4]triazoles, 1,2,4-triazolo[2,1-b][1,3,4]thiadiazoles and 3-phenyl-s-triazolo[3,4-b][1,3,4]thiadiazines using ketones containing active methyl or methylene group, in short reaction times and good reaction yields (Figure 1).

![Figure 1. Thiazolotriazole and thiadiazine derivatives.](image)

In our laboratory, we discovered that acidified acetic acid condition (AcOH/H⁺), which we apply here, for synthesis of a variety of multifunctional compounds possess distinct advantages such as short reaction time, one-pot reaction, using cyano compounds containing active methylene group directly which are safe and cheap materials, without formation of highly toxic, irritant and dangerous halocyano derivatives. Further the syntheses afforded products with an amino group adjacent to the ester or amide group at the 5- and 6-positions of the thiazolo[3,2-b][1,2,4]triazole, which could not be obtained using the classical methods. Also, the acidified acetic acid conditions could be used for synthesis of thiazolo[3,2-b][1,2,4]triazol-5(6H)-one.
directly. Here we describe our attempts to generalize this reaction so that it can be applied for the synthesis of multifunctional fused heterocycles.

**Results and Discussion**

On heating of 5-mercapto-3-phenyl-s-triazole 8 under reflux with cyano compounds containing active methylene group such as ethyl cyanoacetate, cyanoacetamide and malononitrile 9a-c using the acidified acetic acid method (AcOH/H⁺), 5-amino-2-phenyl-6-substituted[1,3]thiazolo[3,2-b][1,2,4]triazoles 10a,b were obtained in 30 - 50 % yields (Scheme 1).

![Scheme 1. Reaction of 5-mercapto-3-phenyl-s-triazole 8 with compounds containing an active methylene.](image)

R = a; COOEt, b; CONH₂, c; CN

The structures of compounds 10a,b were confirmed on the basis of their elemental analysis, IR, ¹H-NMR and mass spectral analysis. The IR spectra of compounds 10a showed bands at 3400-3300 cm⁻¹ (NH₂) and 1680 cm⁻¹ (C=O ester), while 10b showed bands at 3400-3190 cm⁻¹ (NH₂) and 1660 cm⁻¹ (C=O amide) besides the expected bands. The ¹H-NMR spectra of compounds 10a,b were characterized by the appearance of multiple signals at δ 7.4-8.1 attributed to the aromatic protons, in addition the compound 10a showed a triplet signal at δ 1.1 and a quartet signal at δ 4.2 attributed to ethyl group. The mass spectra of 10a,b showed the molecular ion peaks at m/z 288.7 (100%) and 259.1 (100%) respectively. Further, the structure of compound 10b was confirmed by unequivocal synthesis via the reaction of 8 with bromocyanoacetamide in an aqueous solution of potassium hydroxide (Scheme 2).

![Scheme 2. Reaction of 5-mercapto-3-phenyl-s-triazole 8 with bromocyanoacetamide.](image)

The proposed reaction mechanism is summarized in Scheme 1. It may proceed via the formation of dimeric disulfide 11 followed by nucleophilic attack by the imine form on the
dimeric disulfide to give the carbonium ion 12, which undergoes intramolecular cyclization to produce the cyclized imino structures 13. Protonation of 13 in the presence of acid medium gives the cyclized carbonium ion 14 followed by deportation to yield the cyclized compounds 10a,b as shown in the following (Scheme 3).

Scheme 3. Reaction mechanism of formation of compounds 10a,b.

The suggested mechanism45 is supported by formation of disulfide 11 in 81% yield on refluxing the 5-mercapto-3-phenyl-s-triazole 8 in acetic acid in the presence of concentrated sulfuric acid in the absence of an active methylene compound.44 The formation of compound 10b showed that the cyano group of 10c undergoes hydrolysis to the corresponding amide.

Interaction of 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazolo-6-carboxamide 10b with triethyl orthoformate, acetic anhydride, benzaldehyde in the presence of piperidine (or benzoyl chloride) and carbon disulfide in alcoholic potassium hydroxide afforded 2-phenyl[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one 15 in 53% yield, 6-methyl-2-phenyl[1,2,4]triazolo[2',3':3,2] [1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one 16 in 60% yield, 2,6-diphenyl[1,2,4]triazolo[2',3':3,2] [1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one 17 in 45% yield and 2-phenyl-6-thioxo[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one 18 in 52% yield, respectively as shown in Scheme 4.

The structures of compounds 15-18 were confirmed on the basis of their elemental analysis, IR, $^1$H-NMR, $^{13}$C-NMR and the mass spectral data. The IR spectra lacked the amino (NH$_2$) and amide (CONH$_2$) absorption peaks and showed bands at 3150-3050 cm$^{-1}$ (NH aromatic), 2998-2980 cm$^{-1}$ (CH aliphatic), 1680-1659 cm$^{-1}$ (C=O), 1537-1516 cm$^{-1}$ (C=N) and the aromatic skeleton bands at 1481-1450 cm$^{-1}$. The $^1$H-NMR spectra of compounds 15-18 were characterized by the appearance of multiple signals at $\delta$ 7.5-8.2 ppm attributed to the aromatic protons and single broad signal at $\delta$ 13.4-13.6 ppm attributed to NH, in addition compounds 15 and 16 showed two singlet signals at $\delta$ 8.6 and 2.0 ppm attributed to CH and methyl group respectively. The $^{13}$C-NMR spectra of compounds 15-18 in DMSO-$d_6$ showed signals at $\delta$ 166.81-167.75 ppm attributed to the carbonyl groups, in addition to the other carbons at the expected chemical shifts. The mass spectra of 15-18 showed the molecular ion peaks $M^+$ at 269.9 (100%), 283.9 (100%), 345.6 (0.55%) and 301.8 (1.7%) respectively.

Reaction of 5-mercapto-3-phenyl-1,2,4-triazole 8 with chloroacetonitrile and benzaldehyde in boiling acidified acetic acid afforded directly one pure product, which was identified as 19 rather than 20 (Scheme 5).

The formation of 19 can be explained by S-alkylation of 8 followed by intramolecular cyclization via nucleophilic attack of NH to the cyano group to form the cyclized imine derivative 22, which undergoes hydrolysis to the ketone 23 followed by condensation with benzaldehyde to give the product. The intermiediacy of ketone 23 was verified by refluxing 8 with chloroacetic acid and benzaldehyde or by refluxing 2-[(5-phenyl[1,2,4]triazolo-3-yl)thio]acetonitrile/acetic acid 21a,b, which were prepared by the reaction of 3-phenyl-5-mercapto-1,2,4-triazole 8 with chloroacetic acid or chloroacetonitrile in alcoholic potassium
hydroxide solution, and benzaldehyde under the same reaction conditions, both of which also gave product 19 (Scheme 6).

Scheme 5. Reaction of mercaptotriazole 8 with chloroacetonitrile.

Scheme 6. Reaction of triazolethioacetonitrile and triazole thioacetic acid with PhCHO using acidified acetic acid condition.
Based on the previously reported studies using similar compounds,\textsuperscript{46,47} the higher nucleophilicity of N-2 than N-4 due to the alpha N effect. Molecular modeling calculations (MM2) indicated that isomer 19 is more stable than 20, while the E-isomer (HF = 137.64 kcal/mol) of 19 is more favorable than the Z-isomer (137.65 Kcal/mol), Figure 2.\textsuperscript{47}

![Diagram of isomers 19 and 20](image)

**Figure 2.** Isomers of compounds 19 and 20.

The structures of compounds 19 and 21\textsubscript{a,b} were confirmed on the basis of their elemental analysis and spectral data. The IR of compounds 21\textsubscript{a,b} showed bands at 3270-3175 (NH), 3100-3090 (CH aromatic), 2920 (CH aliphatic), 1550 (C=N) and the aromatic skeleton bands at 1460-1410 cm\textsuperscript{-1}, in addition at 2210 cm\textsuperscript{-1} (C≡N) in compound 21\textsubscript{a} and 1710 cm\textsuperscript{-1} (C=O) in compound 21\textsubscript{b} respectively. The IR spectrum of compound 19 lacked the NH absorption peak and showed the C=O and C=C peaks at 1725 and 1560 cm\textsuperscript{-1} respectively. The \textsuperscript{1}H-NMR spectra of compounds 19, 21\textsubscript{a} and 21\textsubscript{b} showed singlet signals at δ 8.1, 4.15 and 4.05 ppm attributed to (C=CH), (CH\textsubscript{2}CN) and (CH\textsubscript{2}COOH) groups respectively. The mass spectrum of compound 19 showed the molecular ion peak at m/z 305.1 (100%). Further, the structure of compound 19 was chemically confirmed by an alternative synthesis\textsuperscript{46} (Scheme 7).

![Scheme 7](image)

**Scheme 7.** Synthesis of 19 using benzaldehyde and AcOH, Ac\textsubscript{2}O and AcONa.

**Biological activity**

One of the purposes of the present work was to synthesize new heterocyclic compounds which might be of certain biological interest. Some of the newly synthesized compounds were screened
for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were *Serratia marcescens*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli*. For antifungals, *Candida albicans*, *Geotrichum candidum*, *Aspergillus flavus*, *Trichophyton rubrum*, *Scopulariopsis bervicaulis* and *Fusarium oxysporum* were used. Both microbial studies were assessed by minimum inhibitory concentration (MIC) by serial dilution method. For this the compound whose MIC has to be determined was dissolved in serially diluted DMSO, then a standard drop of the culture prepared for the assay was added to each of the dilutions and incubated for 16-18 h at 37 °C (Tables 1 and 2).

**Table 1.** The antibacterial activity (inhibition zone in (mm) and MICs given in brackets) of some selected compounds

<table>
<thead>
<tr>
<th>Sample</th>
<th><em>Serratia marcescens</em></th>
<th><em>Pseudomonas aeruginosa</em></th>
<th><em>Staphylococcus aureus</em></th>
<th><em>Bacillus cereus</em></th>
<th><em>Escherichia coli</em></th>
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<tr>
<td>10a</td>
<td>10(20)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12(20)</td>
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<tr>
<td>10b</td>
<td>10(20)</td>
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<td>12(10)</td>
<td>15(20)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>10(20)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>10(20)</td>
<td>-</td>
<td>-</td>
<td>12(20)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>10(20)</td>
<td>-</td>
<td>-</td>
<td>12(20)</td>
<td></td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CHL*</td>
<td>12(1.25)</td>
<td>14(5.0)</td>
<td>10(1.25)</td>
<td>34(0.3)</td>
<td>12(0.3)</td>
</tr>
</tbody>
</table>

*CHL = Chloramphenicol as standard.

**Table 2.** The antifungal activity (inhibition zone in (mm) and MICs given in brackets) of some selected compounds

<table>
<thead>
<tr>
<th>Sample</th>
<th><em>Candida albicans</em></th>
<th><em>Geotrichum candidum</em></th>
<th><em>Aspergillus flavus</em></th>
<th><em>Trichophyton rubrum</em></th>
<th><em>Scopulariopsis bervicaulis</em></th>
<th><em>Fusarium oxysporum</em></th>
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</thead>
<tbody>
<tr>
<td>10a</td>
<td>-</td>
<td>11(20)</td>
<td>-</td>
<td>10(20)</td>
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<tr>
<td>10b</td>
<td>-</td>
<td>11(20)</td>
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<td>-</td>
<td>12(20)</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>DMSO</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CLO*</td>
<td>25(0.3)</td>
<td>24(0.3)</td>
<td>24(2.5)</td>
<td>36(1.25)</td>
<td>26(2.5)</td>
<td>20(10)</td>
</tr>
</tbody>
</table>

*CLO = Clotrimazole as standard.*
Experimental Section

**General.** Melting points were determined using Gallen Camp melting point apparatus and are uncorrected. IR spectra were measured on a Shimatzu-470 spectrometer using KBr techniques. $^1$H-NMR spectra were measured on a Varian EM-390, 90MHz spectrometer (Spectral Unit, Assiut University, Egypt) or a Bruker DX 400-MHz spectrometer (Department of Physical Chemistry, Geneva) using CDCl$_3$ or DMSO-$d_6$ as a solvent and TMS as internal standard. $^{13}$C NMR spectra were measured on a Bruker DX 400-MHz spectrometer. Mass spectra were recorded on Jeol-Jms-600H spectrometer using the direct inlet system. The elemental analyses were performed using Perkin-Elmer elemental analyzer 240-C.

5-Amino-2-phenyl-6-substituted[1,3]thiazolo[3,2-b][1,2,4]triazoles (10a,b). **General procedure**

A mixture of 5-mercapto-3-phenyl-1,2,4-triazole$^{46}$ 8 (0.88 g, 0.005 mol) and cyano compound 9a-c (0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of concentrated acid (H$_2$SO$_4$) (6-8 drops) was refluxed for 3 h. The reaction mixture was then cooled diluted with H$_2$O (10 mL) and neutralized with NH$_3$ solution. The crude product thus obtained was collected by filtration, washed with H$_2$O (3x) and crystallized from EtOH to give 10a,b as colorless crystals in 30 and 50% yields respectively.

**Ethyl 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxylate (10a).** Yield: 0.43 g (30%), colorless crystals (EtOH), mp 186-188 °C. IR (KBr): ν = 3400-3300 (NH$_2$), 3050 (C–H arom.), 2990 (C–H aliph.), 1680 (C=O), 1628 (C=N), 1489 cm$^{-1}$ (C=C). $^1$H NMR (90 MHz, DMSO-$d_6$): δ = 1.1 (t, $J = 2.7$ Hz, 3H, CH$_2$CH$_3$), 2.1 (s, 2H, NH$_2$), 4.2 (q, $J = 2.7$, 2H, CH$_2$CH$_3$) 7.4–8.1 (m, 5 H, H-arom.). MS (EI, 70 eV): $m/z$ (%) = 288.7 [M$^+$] (100), 259.8 (2), 241.9 (12), 214.9 (31), 189.1 (13), 176.9 (10), 143.9 (12), 102.9 (13), 77.1 (8), 67.9 (4), 56.8 (1). Anal. Calcd for C$_{13}$H$_{12}$N$_4$O$_2$S (288.32): C, 54.15; H, 4.20; N, 19.43; S, 11.12%. Found: C, 53.98; H, 4.11; N, 19.60; S, 11.22%.

5-Amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide (10b). **Method A.** This compound was obtained according to the General Procedures as colorless crystals after crystallization from EtOH, Yield 0.65 g (50%), mp. 290-291 °C. IR (KBr): ν = 3400-3190 (NH$_2$), 3010 (C–H arom.), 2995 (C–H aliph.), 1660 (C=O), 1620 (C=N), 1480 cm$^{-1}$ (C=C). $^1$H NMR (90 MHz, DMSO-$d_6$): δ = 7.2 (s, 2H, NH$_2$), 7.4 (s, 2H, CONH$_2$) 7.5–8.0 (m, 5 H, H-arom.). MS (EI, 70 eV): $m/z$ (%) = 259.1 [M$^+$] (100), 242.1 (41), 216.1 (19), 189.1 (12), 144.1 (18), 103.2 (41), 77.1 (20), 65.1 (3), 56.7 (6). Anal. Calcd for C$_{11}$H$_{9}$N$_5$OS (259.29): C, 50.96; H, 3.50; N, 27.01; S, 12.37%. Found: C, 50.99; H, 3.36; N, 26.97; S, 11.97%.

**Method B.** This compound was obtained from the reaction of bromo cyanoacetamide and compound 8 as follows: A sample of 5-mercapto-3-phenyl-s-triazole 8 (0.88 g, 0.005 mol) was dissolved in an aqueous solution of KOH (0.28 g, 0.005 mol) with continuous stirring at room temperature, then a solution of bromo cyanoacetamide (0.81 g, 0.005 mole) in EtOH was added dropwise over a period of 30 min. The reaction mixture was stirred for further 2 h at room
temperature. The crude product thus obtained was collected by filtration, washed with H$_2$O and crystallized from EtOH to give 10b as colorless needles, yield 1.12 g, (86%), mp 290-291 ºC. The analysis of this compound was in agreement with that obtained using the acidified acetic acid method, Method A.

2-Phenyl[1,2,4]triazolo[2′,3′:3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (15). A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide 10b (1.3 g, 0.005 mol) and triethyl orthoformate (5 mL) in AcOH (10 mL) was refluxed for 2 h. The solid product thus formed was collected by filtration and crystallized from DMF to give 15 as white crystals; Yield 0.71 g (53%), colorless needles (DMF), mp > 360 ºC. IR (KBr): $\nu$ = 3100 (NH), 3060 (C–H arom.), 2998 (C–H aliph.), 1678 (C=O), 1516 (C=N), 1478 (C=C) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 7.5 (t, 3H, H-arom.), 8.2 (d, 2H, H-arom.), 8.6 (s, 1H, CH), 13.4 ppm (s, 1H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ = 167.74 (C=O), 157.87 (C-2=N), 157.77 (C-9a=N), 151.0 (CH), 147.01 (C-4a=C), 131.0 (C-arom.), 130.94 (CH–arom.), 130.47 (C-9a=C), 129.49 (2 CH-arom.), 126.95 (2 CH-arom.). MS (EI, 70 eV): $m/z$ (%) = 269.9 [M+] (100), 230.3 (43), 202.3 (140), 147.2 (5), 103.2 (32), 71.3 (17), 57.3 (17). Anal. Calcd for C$_{12}$H$_7$N$_5$OS (269.28): C, 53.52; H, 2.62; N, 26.01; S, 11.91%. Found: C, 53.22; H, 2.45; N, 25.86; S, 11.67%.

6-Methyl-2-phenyl[1,2,4]triazolo[2′,3′:3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (16). A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide 10b (1.3 g, 0.005 mol) and Ac$_2$O (20 mL) was heated under refluxed for 6 h then, after cooling, the excess Ac$_2$O was removed under reduced pressure to give viscous material which was washed several times with EtOH. The solid product thus formed was collected by filtration and crystallized from (AcOH) to give 16. Yield: 0.85 g (60%), brown needles (AcOH), mp > 360 ºC. IR (KBr): $\nu$ = 3050 (NH), 3000 (C–H arom.), 2985 (C–H aliph.), 1671 (C=O), 1518 (C=N), 1481 (C=C) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 2.0 (s, 3H, CH$_3$), 7.5 (t, 3H, H-arom.), 8.1 (d, 2H, H-arom.), 13.5 ppm (s, 1H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ = 167.00 (C=O), 155.31 (C-2=N), 157.12 (C-9a=N), 157.05 (C-6), 147.01 (C-4a=C), 130.46 (C$_8$a=C), 129.59 (2 CH-arom.), 126.96 (2 CH-arom.), 25.45 (CH$_3$). MS (EI, 70 eV): $m/z$ (%) = 283.9 [M+] (100), 257.9 (19), 241.9 (18), 216.9 (17), 188.8 (25), 176.9 (51) 144.1 (89), 90.9 (18), 76.9 (57), 56.7 (9). Anal. Calcd for C$_{13}$H$_9$N$_5$OS (283.31): C, 55.11; H, 3.20; N, 24.72; S, 11.32%. Found: C, 54.89; H, 3.05; N, 24.96; S, 11.64%.

2,6-Diphenyl[1,2,4]triazolo[2′,3′:3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (17). Method A. A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide 10b (1.3 g, 0.005 mol) and benzaldehyde (0.58 g, 0.0055 mol) and a few drops of piperidine was fused together for 20 min. The solid mass thus formed was treated by addition of EtOH (10 mL) and refluxed for 3 h. The solid product thus formed was collected by filtration to give 17. Yield: 0.71 g (40%), colorless needles (AcOH), mp > 360 ºC. IR (KBr): $\nu$ = 3062 (NH), 3010 (C–H arom.), 1659 (C=O), 1537 (C=N), 1450 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 7.6 (m, 6H, H-arom.), 8.2 (m, 4H, H-arom.), 13.6 (s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 167.75 (C=O), 159.05 (C-2=N), 158.41 (C-9a=N), 158.06 (C-6), 147.12 (C-4a=C), 132.97 (CH-arom.), 131.67 (C-arom.), 131.91(CH-arom.), 130.49 (C-8a=C), 129.47 (4CH-arom.), 129.33 (C–
arom.), 128.80 (2 CH-arom.), 126.99 ppm (2 CH-arom.). MS (EI, 70 eV): m/z (%) = 345.6 [M+]
(1), 300.7 (100), 254.7 (37), 200.8 (33), 148.6 (2), 103.8 (3), 92.9 (3), 77.8 (2), 68.9 (10), 56.9
(8). Anal. Calcd for C18H11N5OS (345.38): C, 62.60; H, 3.21; N, 20.28; S, 9.28%. Found: C,
62.45; H, 3.54; N, 20.11; S, 9.36%.

Method B. A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide (10b; 1.3 g, 0.005 mol) and benzyol chloride (5 mL) was refluxed for 1 h then, after cooling, the
reacion mixture was treated with petroleum ether and the product thus formed was collected by
filtration and crystallized from AcOH to give 17 as colorless needles, yield 0.81 g, 46%, mp >
360 °C. The analysis of this compound was in satisfactorily agreement with that obtained in
Method A.

2-Phenyl-6-thioxo[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (18). A
mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide 10b (1.3 g, 0.005
mol), CS2 (5 mL) and KOH (0.31 g, 0.0055 mol) in EtOH (20 mL) was refluxed for 4 h. The
reaction mixture was then cooled, diluted with cold H2O and acidified with AcOH. The
precipitate thus formed was collected by filtration, washed with H2O several times to give 18.
Yield: 0.78 g (52%), brown needles (AcOH), mp 320 °C. IR (KBr): ν = 3150-3070 (2 NH), 3010
(C–H arom.), 1680 (C=O), 1650 (C=S), 1520 (C=N), 1470 cm –1 (C=C). 1H NMR (400 MHz,
DMSO-d6): δ = 2.1 (s, 1H, NH), 7.0 (t, 3H, H-arom.), 8.1 (d, 2H, H-arom.), 12.3 ppm (s, 1H,
NH). 13C NMR (400 MHz, DMSO-d6): δ = 172.9 (C=S), 166.81 (C=O), 155.30 (C-2=N), 157.51
(C-9a=N), 147.10 (C-4a=C), 130.91 (C-arom.), 130.50 (CH–arom.), 129.49 (C8a=C), 129.14 (2
CH-arom.), 127.01 (2 CH-arom.). MS (EI, 70 eV): m/z (%) = 301.8 [M +] (2), 290.1 (5), 255.7
(36), 234.9 (2), 225.8 (3), 223.7 (9), 191.9 (18), 177.2 (40), 160.1 (23), 127.9 (22), 118.7 (11),
104.1 (12), 95.8 (15), 75.9 (100), 63.8 (52), 56.8 (4). Anal. Calcd for C12H7N5OS2 (301.35): C,
47.83; H, 2.34; N, 23.24; S, 21.28%. Found: C, 47.49; H, 2.13; N, 23.55; S, 21.63%.

(E)-6-Benzylidene-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazol-5(6H)-one (19). Method A. A
mixture of 5-mercapto-3-phenyl-1,2,4-triazole 8 (0.88 g, 0.005 mol) and benzaldehyde (0.53 g,
0.005 mol) and chloroacetonitrile (0.38 g, 0.005 mol) in glacial AcOH (25 mL) and a catalytic
amount of conc. H2SO4 was refluxed 5 h. The mixture was concentrated, followed by addition of
cold H2O (10 mL) and neutralized with NH3 soln. The crude product thus obtained was
collected by filtration, washed with H2O to give 19. Yield: 1.10 g (70%), brown needles (AcOH), mp 230–
231 °C (reported mp 230–231 °C46). IR (KBr): ν = 3050 (C–H arom.), 1560 (C=N), 1490 cm–1 (C=C). 1H NMR (90 MHz, CDCl3): δ = 7.4–8.1 (m, 10H, H-
arom.), 8.1 ppm (s, 1H, CH). MS (EI, 70 eV): m/z (%) = 305.1 [M+] (100), 276.7 (2), 11.1 (2),
173.8 (7), 146.8 (4), 133.9 (12), 102.9 (25), 76.1 (3), 56.8 (1). Anal. Calcd for C17H11N3OS
(305.35): C, 66.87; H, 3.63; N, 13.76; S, 10.50%. Found: C, 66.16; H, 3.76; N, 13.80; S, 10.18%.

Method B. A mixture of [(5-phenyl-1,2,4-triazolo-3-yl)thio]acetonitrile/acetic acid 21a,b (0.005
mol) and benzaldehyde (0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of conc.
H2SO4 (6–8 drops) was refluxed for 5 h. The solvent was concentrated, followed by addition of
cold H2O (10 mL) and neutralized with NH3 solution. The crude product thus obtained was
collected by filtration, washed with H2O and crystallized from AcOH to give 19 as brown
needles in, yield 1.29 g, 85% (from 21a) and 1.22 g, 80% yield (from 21b) respectively, mp 230-231 ºC. The analysis of this compound was in agreement with that obtained using the acidified acetic acid method.

[(5-Phenyl-1,2,4-triazolo-3-yl)thio]acetonitrile/acetic acid (21a,b). General procedure
To a solution of 5-mercapto-3-phenyl-1,2,4-triazole 8 (0.88 g, 0.005 mol) in absolute EtOH (15 mL) and KOH (0.56 g, 0.01 mol), a solution of chloroacetonitrile or chloroacetic acid (0.0055 mol) in absolute EtOH (5 mL) was added dropwise with stirring. The reaction mixture was stirred at room temperature for a further 30 min, followed by refluxing for 1 h. The precipitated KCl was filtered off. The excess solvent was removed from the mixture by evaporation under vacuum and the residue was treated with H2O. The crude product thus formed was collected by filtration and crystallized from (EtOH) to give 21a,b as colorless needles.

(5-Phenyl-1,2,4-triazolo-3-yl)thioacetonitrile (21a). Yield: 1.10 g (92%), colorless needles (EtOH), mp 168-170 ºC. IR (KBr): $\nu = 3175$ (NH), 3090 (C–H arom.), 2885 (C–H aliph.), 2210 (C≡N), 1550 (C=N), 1410 cm –1 (C=C). $^1$H NMR (90 MHz, CDCl3): $\delta = 4.15$ (s, 2H, CH2), 7.6–8.1 (m, 5 H, H-arom.), 11.6 ppm (s, 1H, NH). Anal. Calcd for C10H8N4S (216.26): C, 55.54; H, 3.73; N, 25.91; S, 14.83%. Found: C, 55.44; H, 3.89; N, 25.67; S, 15.01%.

(5-Phenyl-1,2,4-triazolo-3-yl)thioacetic acid (21b). Yield: 1.10 g (91%); colorless needles (EtOH), mp 180-182 ºC. Lit. 179 ºC.49 IR (KBr): $\nu = 3270$ (NH), 3100 (C–H arom.), 2992 (C–H aliph.), 1710 (C=O), 1550 (C=N), 1460 cm –1 (C=C). $^1$H NMR (90 MHz, CDCl3): $\delta = 4.05$ (s, 2H, CH2), 7.2–8.0 (m, 5 H, H-arom.), 11.50 ppm (s, 1H, NH). Anal. Calcd for C10H9N3O2S (235.26): C, 51.05; H, 3.86; N, 17.86; S, 13.63%. Found: C, 50.88; H, 4.12; N, 17.36; S, 13.55%.

References

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