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One pot synthesis of novel thiazolo[3,2-b][1,2,4]triazoles: A useful synthetic application of the acidified acetic acid method

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RESEARCH ARTICLE

One pot synthesis of novel thiazolo[3,2-b][1,2,4]triazoles: A useful synthetic application of the acidified acetic acid method

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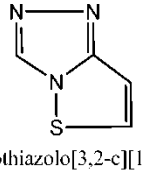
Thiazolo[3,2-b][1,2,4]triazoles and some of its analogues were firstly synthesized starting from 3-benzyl-1,2,4-triazole-5-thiol (**13**). 3-Benzyl-1,2,4-triazole-5-thiol (**13**) was synthesized and reacted with aromatic ketones using the acidified acetic acid method ($AcOH/H^+$) to give directly the cyclized 5-aryl-2-benzyl-1,3-thiazolo[3,2-b][1,2,4]triazoles (**15a-f**) rather the thioketones **14**. The isomeric 2-benzyl[2,3-c]-1,2,4-triazoles **16** could not be obtained using this method. The reaction of 1-phenylacetyl-3-thiosemicarbazide (**17**) with phenyl bromomethyl ketones in refluxing ethanol afforded the 2-(phenylacetyl-hydrazino)-4-phenylthiazole (**18**) which, cyclized into **16a** upon refluxing in $POCl_3$. The tricyclic system **20a–d** was successfully prepared in one pot reaction using the acidified acetic acid in high reaction yield and short reaction time. Formation of both **15a–l** and or **16a–c** was assigned by the molecular minimization energy (MME) calculations which indicated that the formation of **15** is more favorable than the isomeric compounds **16**. Examination of the biological activity against the selected bacteria and fungi revealed that the title compounds possess significant growth promoting effect.

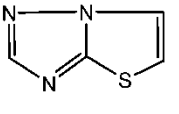
Keywords: Thiazolotriazoles; Synthesis; Acidified acetic acid method; Cyclocondensation; MME calculations and biological activity

1. Introduction

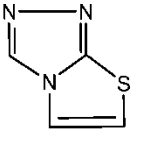
The thiazolo-1,2,4-triazoles are those compounds which contain two fused rings of thiazole and triazole. To the best of our knowledge there are three systems of this class investigated in literature, scheme 1 [1].



isothiazolo[3,2-c][1,2,4]triazole



thiazolo[3,2-b][1,2,4]triazole



thiazolo[2,3-c][1,2,4]triazole

SCHEME 1

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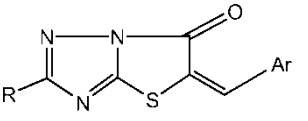
It has been reported that the synthesis of 1,3-thiazolo-1,2,4-triazoles occurred by reaction of the 3-mercapto-5-methyl-1,2,4-triazole **1** (R = CH_3) with chloroacetic acid to give the 1,2,4-triazolylthioglycolic acid intermediate (R = CH_3). Ring closure of this intermediate to the corresponding 3-methyl-1,3-thiazolo[2,3-c][1,2,4]triazol-5(6H)-one **3** (R = CH_3) was achieved by dehydrative cyclization with acetic anhydride in the presence of pyridine. No vigorous proof was given to exclude the possible alternative structure 1,3-thiazolo[2,3-b][1,2,4]triazole **2**, scheme 2 [2].

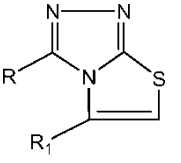
Thiazolo[3,2-b][1,2,4]triazoles have been synthesized and studied by several chemists and their cyclization were also investigated [3–6]. Gogoi *et al.* [7] have prepared the 2-(2,4-dichlorophenyl)thiazolo[3,2-b][1,2,4]triazol-5-(6H)-ones (**4**) in two steps reaction mechanism. Whereas, Tozkoparan [8–14] and coworkers have prepared directly several derivatives of compounds **4** in one step reaction using the mercaptotriazole, chloroacetic acid and aromatic aldehydes.



4

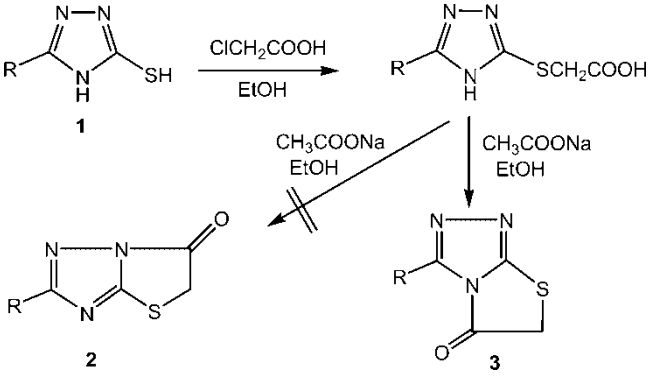
R = CH_3; Ar = Ph, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$

It has been reported that 3-substituted-1,3-thiazolo[2,3-c][1,2,4]triazoles **5** could be obtained from 2-hydrazino-1,3-thiazoles by cyclization of the latter compound using $POCl_3$ as a dehydrating agent [3,15–17].



5

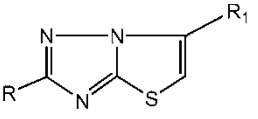
Jean-Luc Bernier *et al.* [18] have prepared 1,3-thiazolo[2,3-c][1,2,4]triazoles *via* cyclocondensation reaction of acetone thiosemicarbazone with phosphonium salt in the presence of formic acid. Thiazolo[3,2-b][1,2,4]triazoles **6** have been synthesized by propargylation of



1 **2** **3**

SCHEME 2

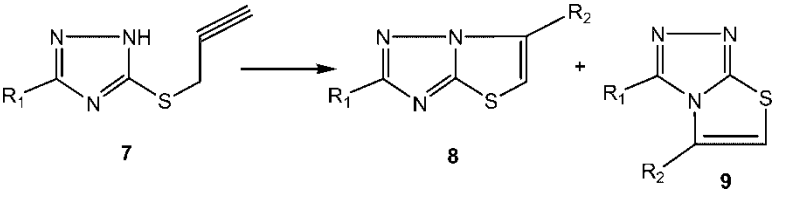
3-aryl-1,2,4-triazole-5-thiones (**1**) in the presence of aqueous sodium hydroxide solution [19].



6

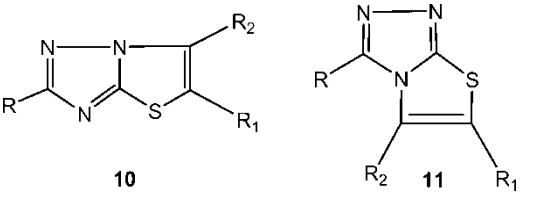
R = C_6H_5, 2-ClC_6H_4, 3-ClC_6H_4,
2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 3-$OCH_3C_6H_4$
R_1 = CH_3

Moreover, Saburo *et al.* [20] have isolated the thiazolo[3,2-b][1,2,4]triazole **8** (R = H, Me; $R^1 = CH_3$) by treating the hydrogen bromide salt of the compound **7** (R = H, Me) with sodium hydroxide solution. While, Mignot *et al.* [21] have reported that, heating of $HClO_4$ salt of compound **7** in acidic or alkaline medium gave a mixture of the isomeric thiazolo[3,2-b][1,2,4]triazole **8** and thiazolo[2,3-c][1,2,4]triazole **9** (R = Ph, 2-$CH_3OC_6H_4$, 3-$CH_3OC_6H_4$; $R^1 = CH_3$). Recently, Heravi *et al.* [22–24] have prepared **8** (R = alkyl, aryl; $R^1 = CH_3$) from **7** using H_2SO_4 or zeolite derivatives as catalyst (scheme 3).



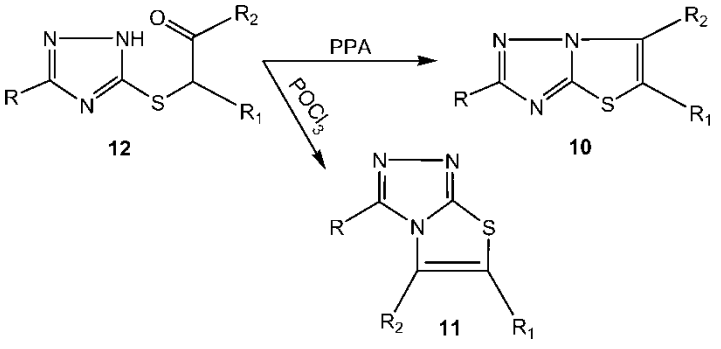
SCHEME 3

To the best of our knowledge the title compounds were obtained by two main routes according to a literature survey, via reaction of 2-imino-3-aminothiazolines with acids [25], anhydrides [1c] or phosgene immonium chloride [27], or cyclization of 2-acylamino-3-aminothiazolines [1d] derivatives. This route provides an unequivocal synthesis of thiazolo[3,2-b][1,2,4]triazole **10**, while cyclization of 2-acylhydrazinothiazoles gave the other isomeric thiazolo[2,3-c][1,2,4]triazoles **11** [1,15].



The second route in which the thiazole ring is built onto a triazole ring *via* reaction of 3-mercapto-1,2,4-triazole (**1**) with α-halo-ketones to give **10** directly or by subsequent cyclization of the thiomethylketone intermediate **12** using PPA or $POCl_3$ which may be led to the formation of thiazolo[3,2-b][1,2,4]triazole **10** or thiazolo[2,3-c][1,2,4]triazole **11** according to the reaction conditions and the nature of 5-substituent in 3-mercapto-1,2,4-triazoles **1**. In general, this route was preferred instead of the previous one as the starting material 3-mercapto-1,2,4-triazoles (**1**) could be easily obtained, scheme 4.

The thiazole nucleus is present in various molecules having biological activity [27–39], and as well, the 1,2,4-triazole moiety takes a part of antiflogistic and antipyretic compounds [40–45]. Such activities have been also found in molecules containing the fused



SCHEME 4

thiazolo-triazole bicyclic system [17,40]. Within this respect and in continuation of our work on these types of reactions [46,47], we planned to synthesize a new heterocyclic compounds in which the 1,2,4-triazole nucleus is fused with other heterocyclic rings using new methods in the hope that resulting compounds would have more potent biological activities.

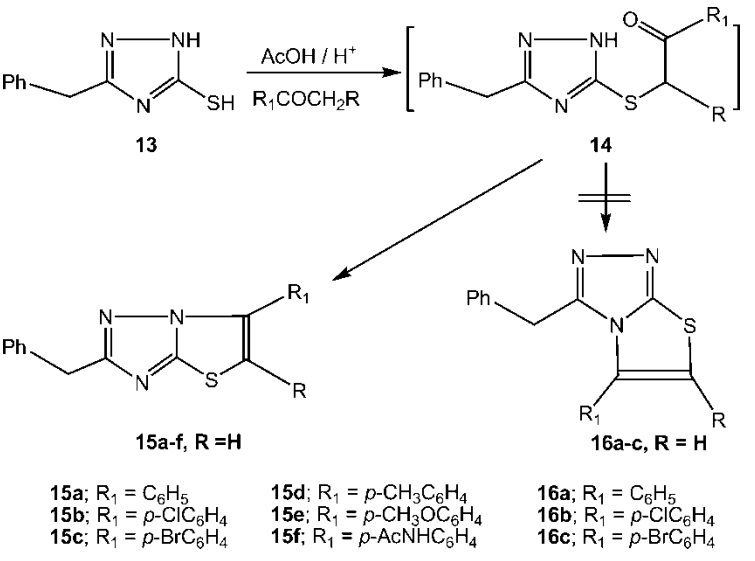
We report herein a versatile novel one step synthesis of hitherto unknown 2-benzylthiazolo[3,2-b][1,2,4]triazole derivatives, which was used to prepare thiazolo[3,2-a]benzimidazoles [46] and imidazo[2,1-b]thiazoles [47]. In our laboratory, the new method has the distinct advantage of dispensing with the use of chemicals like phenyl bromomethyl ketones and alkyl bromide derivatives which are highly toxic, irritable and not easy to prepare. Further, the synthesis affords a variety of substitution on 5 and 6 positions of the 2-benzylthiazolo[3,2-b][1,2,4]triazole derivatives which could not be obtained using the classical methods. Also, it is considered not only the simplest, but also the most cheap and efficient method. Finally, it is considered also as an effective route to design the targeted thiazolo[3,2-b][1,2,4]triazole needed. Consequently, we use this new method to prepare the 2-benzylthiazolo[3,2-b][1,2,4]triazoles, which is preferred over all the literature methods. In this study, 3-benzyl-1,2,4-triazole-5(1H)-thiol (**13**) [48] was condensed with a variety of ketones, containing active methyl or methylene group, by refluxing in acetic acid in the presence of concentrated sulfuric acid.

2. Results and discussion

Refluxing of 3-benzyl-s-triazole-5(1H)-thiol (**13**) with aromatic ketones using the acidified acetic acid method in the presence of catalytic amounts of sulfuric acid gave directly the cyclized products 5-aryl-2-benzyl-1,3-thiazolo[3,2-b][1,2,4]triazoles (**15a–f**) but neither the uncyclized ketones **14** nor the isomeric 2-benzyl[2,3-c][1,2,4]triazoles **16a–c** were obtained, scheme 5.

The structure of **15a–f** was confirmed on the basis of their elemental and spectral analysis; details of the spectra were summarized in the experimental section. The ^{1}H-NMR and mass spectral data were not much help to distinguish the structure of these two isomers **15** or **16**. However, the reaction products were assigned the structure **15** rather than **16** based on these facts; **a**) cyclization of the intermediate ketones **14** following the reported methods for similar compounds, **b**) the unequivocal synthesis of the other isomer **16**, **c**) molecular mechanics calculations (MME) were performed using the computer program PC MODEL 486 version 5 available from Serena Software.

In this context we compare between the literature methods for the synthesis of thiazolo[3,2-b][1,2,4]triazoles and the method we have recently discovered [46,47] for the



SCHEME 5

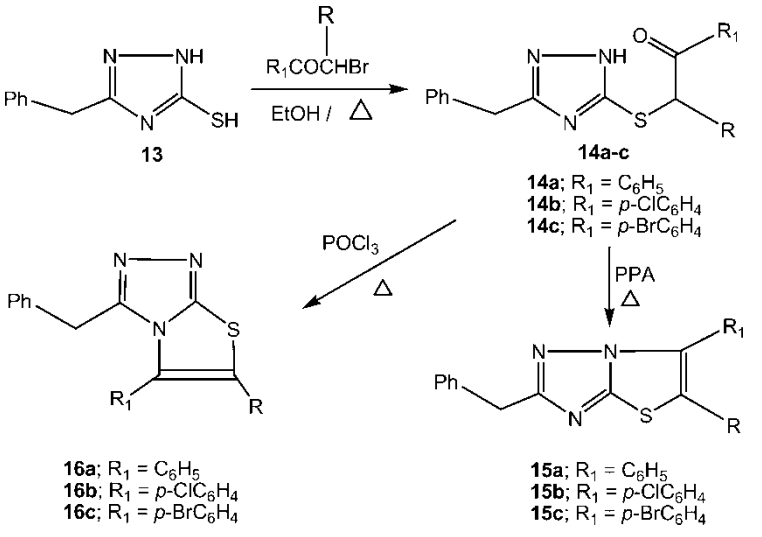
synthesis of the unreported 2-benzyl-1,3-thiazolo[3,2-b][1,2,4]triazoles **15a–l**. This is to proof how our method can be used on multi scale and how easy to prepare several thiazolotriazoles from simple ketones which difficult to apply the literature methods to be synthesized. The synthesis of thiazolo[3,2-b][1,2,4]triazoles **15** and thiazolo[2,3-c]-[1,2,4]triazoles **16** can be achieved according to the following methods.

2.1 *Synthesis of 2-benzyl-1,3-thiazolo[3,2-b][1,2,4]triazoles (15a–c) following the reported methods*

On treatment of **13** with phenyl bromomethyl ketones in refluxing ethanol gave the uncyclized thioketone derivatives **14a–c** as previously described by Czarnocka *et al.* [49] not the cyclized products as previously described with some 3-aryl-5-mercapto-1,2,4-triazoles, scheme 6 [4, 50].

The structure of **14a–c** was confirmed by both elemental analysis and spectral data. The IR spectra of **14a–c** showed strong bands at 3250–3200 and 1680–1660 cm^{-1} characteristic for (NH) and (C=O) groups, respectively. The ^{1}H-NMR spectra of **14a–c** in $CDCl_3$ were in agreement with the proposed structures. Thioketones **14a–c** cyclized into 2-benzyl-1,3-thiazolo-[3,2-b][1,2,4]triazoles **15a–c** on refluxing with polyphosphoric acid (PPA) following the reported methods for similar compounds, scheme 6 [6,51–55].

Moreover, thioketones **14a–c** were cyclized using phosphoryl chloride ($POCl_3$) to give 5-aryl-3-benzyl-1,3-thiazolo[2,3-c][1,2,4]triazoles (**16a–c**) as previously described by many authors for similar compounds [56,57]. This behavior may be attributed to the formation of an intermediate phosphorous compound with the more basic center N_1 or N_2 which favor the cyclization with N_4 to give **16** instead of **15**, this because the presence of $POCl_3$, the N_2 is protonated and become more acidic rather than N_4, scheme 6 [1]. The IR spectra of **16b,c** showed the disappearance of the carbonyl absorption band which supports their cyclic structure. The ^{1}H-NMR spectra of **16b,c** in $CDCl_3$ showed the expected chemical shifts. Compound **16a**, which prepared by this method was identical with that obtained by cyclization



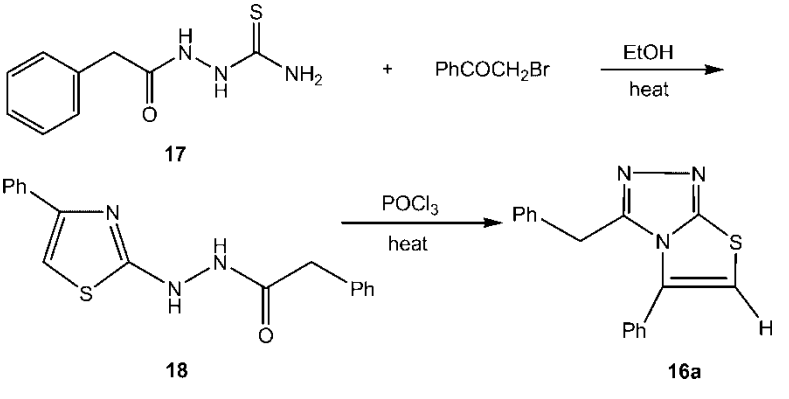
SCHEME 6

of **18** using $POCl_3$ as cyclizing agent. The mass spectra of **15a–c** showed the molecular ion peaks M^+ at m/z 291 (100%), 325, 327 (100%, 37%) and 369, 371 (100%, 95%), respectively.

2.2 *The unequivocal synthesis of 5-aryl-3-benzyl-1,3-thiazolo[2,3-c][1,2,4]triazoles (16a)*

A mixture of 1-phenylacetyl-3-thiosemicarbazide (**17**) and phenyl bromomethyl ketone was refluxed in ethanol to give 2-(phenylacetyl-hydrazino)-4-phenylthiazole (**18**). Refluxing of **18** in $POCl_3$ afforded the isomeric 3-benzyl-5-phenyl-1,3-thiazolo[2,3-c]-[1,2,4]triazole **16a** as previously reported for similar compounds, scheme 7 [50–53].

The synthesized compounds **16a–c** were found to be different on comparison with the isomeric compounds **15a–c**, in term of melting temperature, mixed melting temperature, thin layer chromatography (TLC), IR and ^{1}H-NMR spectra, suggesting the other isomeric structure **16** to them. Consequently, it can be concluded that the application of the acidified acetic



SCHEME 7

acid method, for synthesis of thiazolo-1,2,4-triazoles, led to the formation of thiazolo[3,2-b]-[1,2,4]triazoles **15** rather than the isomeric thiazolo[2,3-c]-[1,2,4]triazoles **16**. It was found also the synthesized compounds **15a–c** using the literature method were identical with those obtained by our method.

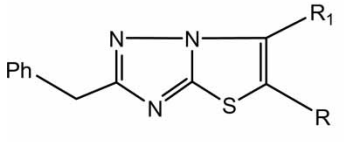
2.3 *Molecular mechanical calculations (MME) study*

Further, the assignment of compounds **15** has been confirmed on the basis of molecular minimization energy (MME) calculations. This study proved that thiazolo[3,2-b]-[1,2,4]triazoles **15** have less energy than the other isomeric compounds **16**. These results indicated that the molecular minimization energy (MME) favors the formation of **15** rather than the isomeric compounds **16**. The molecular minimization energy (MME) calculations are summarized in tables 1 and 2.

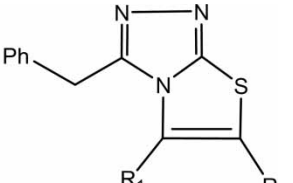
Therefore, refluxing of 3-benzyl-1,2,4-triazole-5-thiol (**13**) with aliphatic ketones containing active methylene group such as propanone, 2-butanone, 2-pentanone, 4-heptanone, acetylacetone and benzoylacetone in acidified acetic acid afforded 5,6-disubstituted-2-benzylthiazolo[3,2-b][1,2,4]triazoles **15 g–l**, respectively, scheme 8.

It is noteworthy that interaction of triazole **13** with ethyl acetoacetate gave a product its IR spectrum lacked the carbonyl group while its ^{1}H-NMR spectrum showed the aromatic protons at 7.40–7.11 (m, 5H) and three signals at δ 6.40 (s, 1H, C-H), 4.15 (s, 2H, CH_2)

Table 1. Molecular mechanical calculations (MME) of compounds 15a–l and 16a–l.



15a–k

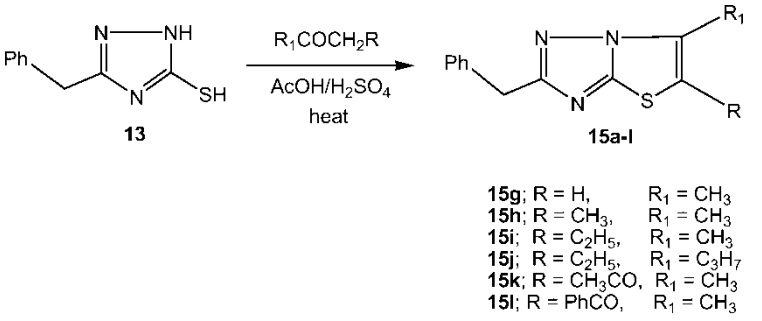


16a–k

Compounds **15a–l** & **16a–l**	R_1	R	*E* (k.cal./mol.) **15a–l**	*E* (k.cal./mol.) **16a–l**
a	C_6H_5	H	51.277	53.687
b	4-ClC_6H_4	H	51.115	54.057
c	4-BrC_6H_4	H	51.093	53.146
d	4-$CH_3C_6H_4$	H	51.417	51.616
e	4-$CH_3OC_6H_4$	H	53.502	53.844
f	4-$AcNHC_6H_4$	H	54.154	55.578
g	CH_3	H	43.578	45.755
h	CH_3	CH_3	43.115	45.729
i	CH_3	C_2H_5	43.561	46.345
j	$(CH_2)_2CH_3$	C_2H_5	44.923	48.103
k	CH_3	CH_3CO	45.605	47.844

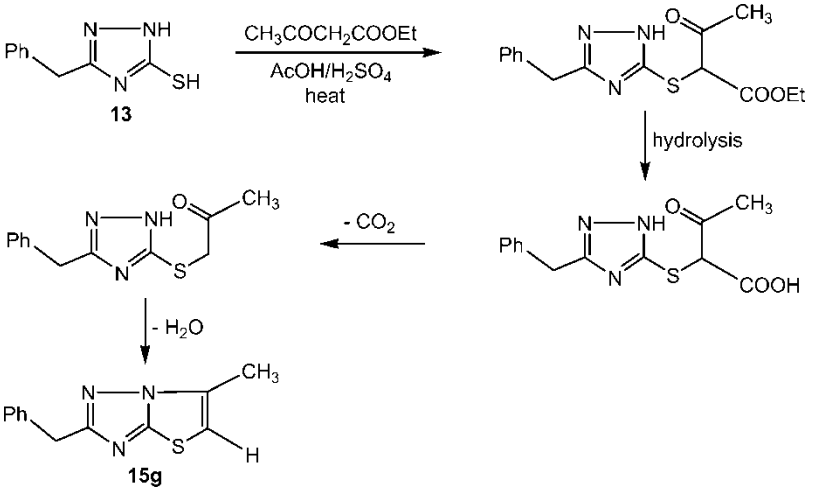
Table 2. Molecular mechanical calculations (MME) of compounds 15a-l.

Isomer	R_1	R	DPM	Torsion	Bend	Stretch	HF	MME
15l	CH_3	COPh	0.15	−5.85	18.07	0.78	133.33	17.13
19	C_6H_5	COMe	1.016	−7.48	18.75	0.81	132.50	17.16



SCHEME 8

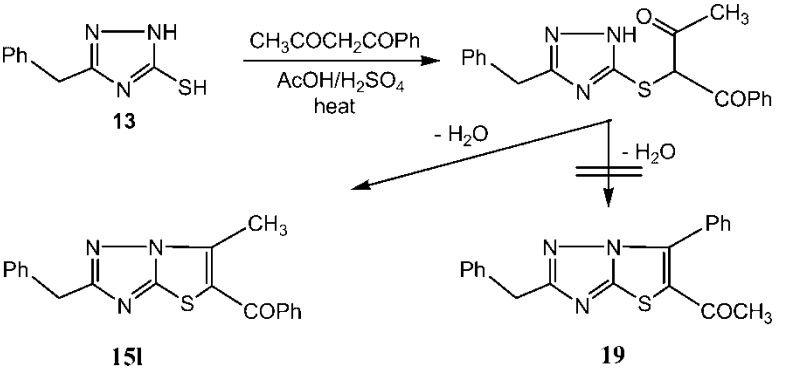
and δ 2.45 ppm (s, 3H, CH_3), but lacked the characteristic ethyl group signals, also the mass spectrum showed the molecular ion peak M^+ at m/z 229 (100%). This compound has been identified as 2-benzyl-5-methyl-1,3-thiazolo[3,2-b][1,2,4]triazole (**15 g**) and is identical with the one prepared from the reaction of triazole **13** with acetone using the acidified acetic acid method. The unexpected compound **15 g** assumed to be formed *via* hydrolysis of the ester group followed by decarboxylation as explained in scheme 9.



SCHEME 9

Further, the interaction of **13** with benzoylacetone presumably led to the formation of two isomers, but the isolated product is only one compound assigned as isomer **15l** rather than isomer **19** as in scheme 10.

However, cyclization of the non-isolable intermediate yielded only one pure product (TLC) and its ^{1}H-NMR spectral data were not of much help in deciding either structure **15l** or **19** was formed. Based on mass spectral fragmentation, structure **15l** was assigned to the cyclized product. Its mass spectrum showed the molecular ion peak M^+ m/z 333 (100%) which on loosing of benzoyl group gave ion at m/z 105 (43%). Also the mass spectrum of **15l** lacks the appearance of the peak at 43 which characterized to the acetyl group ($COCH_3$). The H^1-NMR of **15l** exhibited the appearance of CH_3 group as singlet at δ 2.58 ppm which almost identical to the other methyl groups in compounds **15 g–i** and **15 k**. The minimized energy calculations (MM2) of possible isomers **15l** and **19** were achieved using the Chem3D Ultra 8.0.3 (1985-2003 CambridgeSoft Corporation) (figure 1) and the data are summarized in table 2. From the data it seems that both MME and heat of formation of the isomeric **15l** and **19** are closed



SCHEME 10

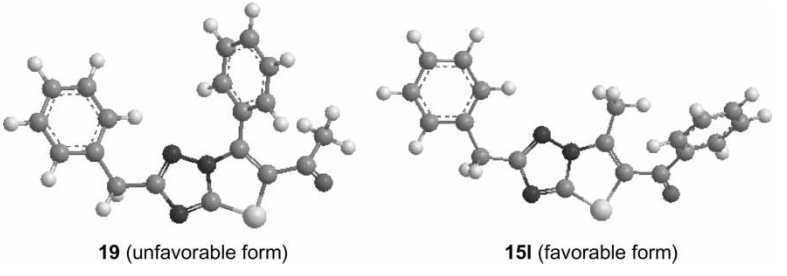
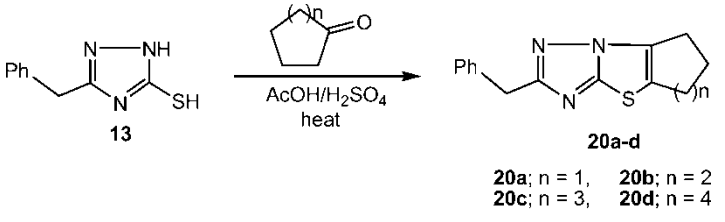


Figure 1. Showed the ball – stick model of possible isomers **15l**.

together and it is difficult to distinguish between them by these calculations. From these facts we can proof that isomer **15l** was formed rather the formation of the isomer **19**.

On the other hand, the synthesis of monohalocyclic ketones is rather much difficult and to isolate these mono-halocyclic ketones probably is problematic. This encouraged us to react the 3-benzyl-1,2,4-triazole-5-thiol (**13**) directly with cyclic ketones such as cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone using the acidified acetic acid method to give the targeted tricyclic system **20a–d**, respectively, scheme 11.

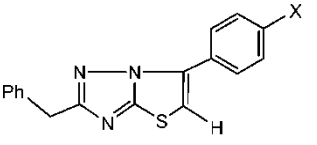


SCHEME 11

The structure of compounds **20a–d** was confirmed on the basis of their elemental and spectral analysis. Details of these data are summarized in the experimental section. The mass spectra of the isomeric compounds **16a–c** were similar to **15a–c**, this illustrate the danger in making structure assignments of isomeric systems based on mass spectral data [34]. In addition, the mass spectra of other compounds, **15f,h,k** and **20a–d** showed the molecular ion peaks M^+ at m/z 348 (100%), 243 (100%), 271 (100%), 255 (100%), 269 (100%), 283 (100%) and 297 (100%), respectively, table 3 and scheme 12.

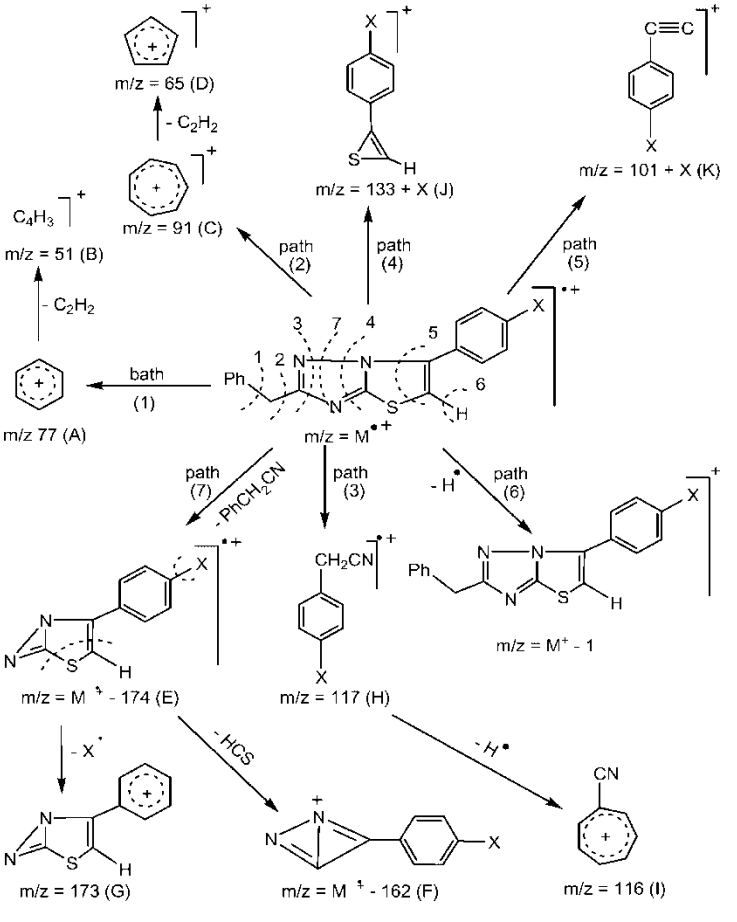
The proposed mechanism of formation of **15a–l** and **20a–d** may be proceed *via* the formation of dimeric disulfide **21** followed by nucleophilic attack by the enol form of the ketones or their acetylated form as shown in scheme 13 [46,58].

Table 3. The mass spectral data of compounds **15a–d**.

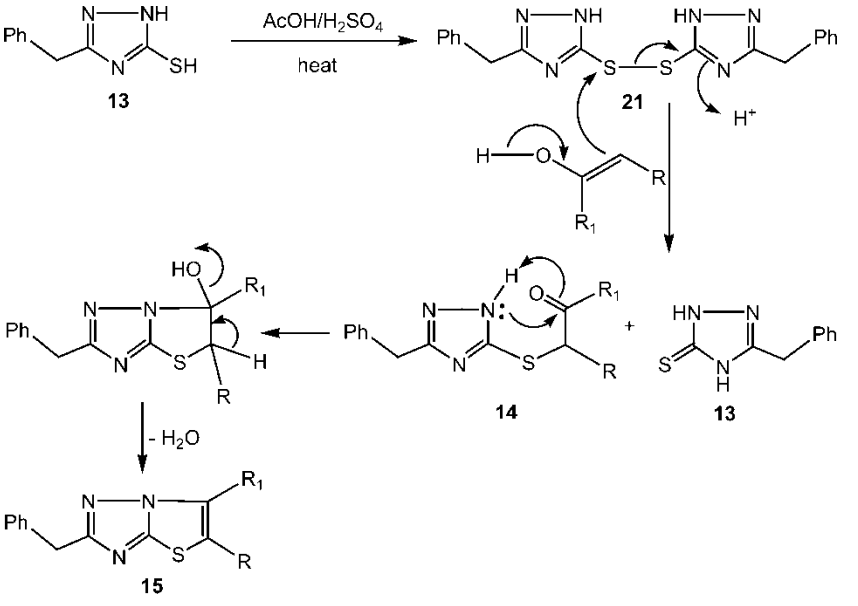


15a–d

No.	X	The molecular ion M^+ and the fragments A-L m/z (%) of the compounds **15a–d**												
		M^+	A	B	C	D	E	F	G	H	I	J	K	L
15a	H	291	77	51	91	65	174	129	173	117	116	134	102	290
		(100)	(16)	(6)	(47)	(8)	(22)	(11)	(5)	(23)	(15)	(50)	(14)	(69)
15b	Cl	325	77	51	91	65	208	163	173	117	116	168	136	324
		(78)	(11)	(9)	(67)	(16)	(4)	(18)	(31)	(40)	(26)	(41)	(17)	(100)
		327					210	165				170	138	326
		(34)					(4)	(5)				(15)	(8)	(83)
15c	Br	369	77	51	91	65	252	207	173	117	116	212	180	368
		(36)	(55)	(57)	(100)	(32)	(–)	(5)	(20)	(29)	(40)	(6)	(9)	(5)
		371					254	209				214	182	370
		(34)					(–)	(4)				(7)	(15)	(9)
15d	CH_3	305	77	51	91	65	188	143	173	117	116	148	116	304
		(100)	(26)	(17)	(70)	(36)	(6)	(15)	(–)	(28)	(35)	(27)	(35)	(30)



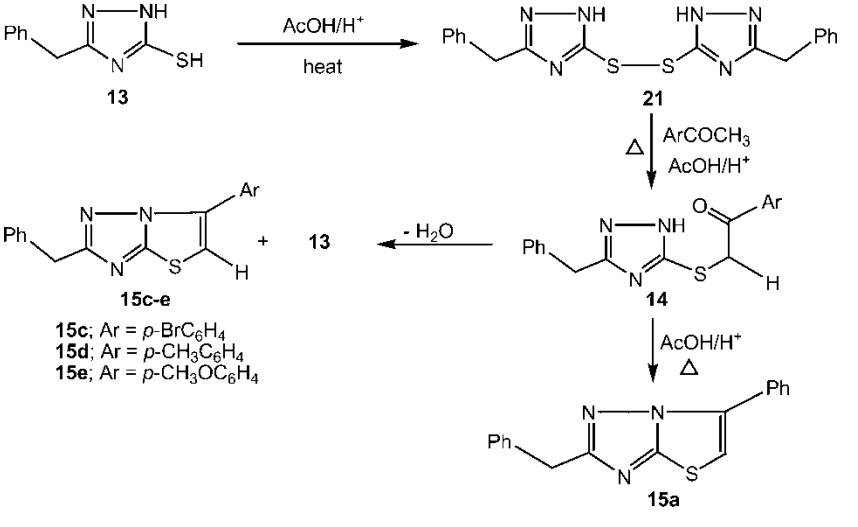
SCHEME 12



SCHEME 13

The suggested reaction mechanism was confirmed chemically by refluxing the 3-benzyl-1,2,4-triazole-5(1H)-thiol **13** in acetic acid in the presence of concentrated sulfuric acid for one hour, the disulphide **21** was obtained after neutralization as needles crystals in 81% yield [58].

The structure of disulphide **21** was established not only on the basis of its elemental analysis but also with spectral data. The reaction of disulphide **21** with ketones such as *p*-bromo, *p*-methyl and/or *p*-methoxyacetophenone under the same reaction conditions yielded the predicted products **15c–e**, respectively as explained in scheme 14. Furthermore, the formation of non isolable intermediate has been confirmed by refluxing of the uncyclized ketone **14a** in acetic acid under the same reaction condition yielded the expected product **15a**, scheme 14.



SCHEME 14

3. Biological Screening

One of the purposes of the present work is to synthesize new heterocyclic compounds that might be of certain biological interest. Accordingly, some of these compounds were selected and screened *in vitro* for their antimicrobial activity against four strains of bacteria table 4.

The antibacterial and antifungal activities of the tested compounds were evaluated by wells method [59] (5 mm) with 10 μL well of (1% concentration) for fungi and 20 microliter/well of (1% concentration) for bacteria using DMSO as a solvent. The inhibition zones (mm) obtained in comparison with those of clotrimazol were summarized in table 4. These results revealed that the most tested compounds were active against most strains of fungi, while all the tested compounds were inactive against Gram +ve and Gram −ve bacteria.

Table 4. The antifungal activity (expressed in growth inhibitory zone) of some selected compounds.

Fungal species Compounds	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)
Clotrimazol	13	15	10	20	20	15	13	10	11	17
DMSO	–	–	–	–	–	–	–	8	–	–
15a	–	–	–	–	–	–	8	10	–	12
15b	–	–	–	–	–	–	–	7	–	–
15c	–	–	–	–	–	–	–	7	–	–
15 g	–	–	10	–	–	18	–	14	–	15
15 h	–	–	10	–	–	28	7	12	–	22
15 k	–	–	–	–	–	8	–	–	–	8
20a	–	–	–	–	–	–	–	–	–	–
20b	–	–	–	–	–	20	–	–	–	10
20d	–	–	–	–	–	–	–	–	–	–
21	–	–	–	–	–	–	–	–	–	–

(a) Aspergillus flavus, (b) Aspergillus fumigatus, (c) Aspergillus Niger, (d) Aspergillus var. Albus, (e) Candida albicoms, (f) Chrysosponium tropicum, (g) Fusarium oxysporum, (h) Geotrichum candidum (i) Microsporum nanum (j) Trichophytom rubrum.

4. Conclusion

The title compounds were synthesized as new compounds with anticipated biological values and their structures were confirmed successfully by spectral and elemental analyses. The versatile novel one step synthesis of these hitherto unknown compounds was derived in our laboratory. This method has the distinct advantage of dispensing with the avoid using highly toxic and irritable materials which are not easy to obtain as well. The use of this method afforded a variety of substitution in 5 and 6 positions of the 2-benzylthiazolo[3,2-b] [1,2,4]triazole derivatives which could not be obtained using the classical methods. Further, it is considered also as an effective route to design the targeted thiazolo[1,2,4]triazoles needed in simplest and most cheap efficient route. In this study, 3-benzyl-1,2,4-triazole-5-thiol (**13**) was synthesized and condensed with a variety of ketones, containing active methyl or methylene group, by refluxing in acetic acid in the presence of sulfuric acid to prepare the 2-benzylthiazolo[3,2-b][1,2,4]triazoles, which is preferred over all the literature methods.

5. Experimental

Melting points were recorded on a Gallencamp melting point apparatus and are uncorrected. Infrared spectra (IR) were measured on a Shimadzu 470 IR spectrometer (KBr, cm^{-1}). ^{1}HNMR Spectra were recorded at room temperature on a Varian EM-390, 90 MHz Spectrometer or on a Jeol LA 400 MHz FT-NMR spectrometer. Chemical shifts are denoted in δ units (ppm), relative to tetramethylsilane (TMS) as internal standard, J values are given in Hz. $CDCl_3$ is used as a deuterated solvent unless otherwise stated. MS Spectra were obtained using a JEOL JMS-600 mass spectrometer. Elemental analyses were recorded on a Perkins Elmer 240C elemental analyzer.

5.1 *Synthesis of 2-(5-benzyl-2H-1,2,4-triazol-3-ylthio)-1-phenyl/4-chlorophenyl/ 4-bromophenyl ethanone (14a–c)*

A mixture of **13** (0.95 g, 5 mmol) and phenyl bromomethyl ketone (6 mmol) in ethanol was refluxed for 3 hours. The reaction mixture was cooled and the precipitate thus formed was collected by filtration and dried. The crude products were crystallized from benzene/ethanol mixture to give the corresponding **14a–c** as needles crystals in high yields.

5.2 *2-(5-benzyl-2H-1,2,4-triazol-3-ylthio)-1-phenylethanone (14a)*

R = C_6H_5. This compound was obtained as needles crystals in 80% yield, Mp. 110–111°C. IR (KBr) ν cm^{-1} = 3290s (NH), 3030s (C-H aromatic), 2940 m, 2900 m (C-H aliphatic), 1670s (C=O), 1580s (C=N), 1560 m, 1510s, 1440s (C-H aromatic), 1280s, 1210s, 1040s 990s, (C-O, C-H, C-N), 760s, 710s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 11.80 (s, 1H, NH*), 8.00–7.21 (m, 10H, aromatic-H), 4.61 (s, 1H, SCH_2), 4.05 (s, 2H, SCH_2). Elemental analysis for $C_{17}H_{15}N_3OS$ (309.39); Calcd: C; 66.00, H; 4.89, N; 13.58, S; 10.36%. Found: C; 65.67, H; 4.53, N; 13.51, S; 9.89%.

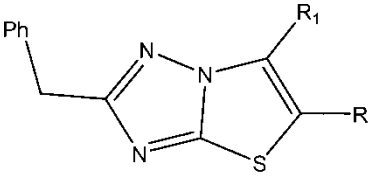
5.3 *2-(5-benzyl-2H-1,2,4-triazol-3-ylthio)-1-(4-chlorophenyl)ethanone (14b)*

R = *p*-ClC_6H_4. This compound was obtained as needles crystals in 82% yield, Mp. 220–222°C. IR (KBr) ν cm^{-1} = 3200 m (NH), 296os, 2950s, 2930s (C-H aromatic), (C-H aliphatic), 1660s (C=O), 1580s, (C=N), 1475s, 1400s, (C-H aromatic), 1305s, 1200s, 1255s, 1050s (C-O, C-H), 750s, 730s, 700s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 11.91 (s, 1H, NH), 8.29–7.30 (m, 9H, aromatic-H), 4.80 (s, 1H, SCH_2), 4.20 (s, 2H, SCH_2). Elemental analysis for $C_{17}H_{14}ClN_3OS$ (343.84); Calcd: C; 59.39, H; 4.10, N; 12.22, S; 9.33%. Found: C; 59.01, H; 4.37, N; 12.16, S; 9.00%.

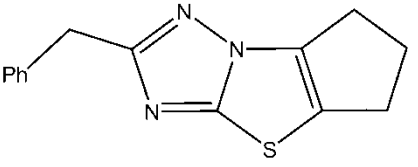
5.4 *2-(5-benzyl-2H-1,2,4-triazol-3-ylthio)-1-(4-bromophenyl)ethanone (14c)*

R = *p*-BrC_6H_4. This compound was obtained as needles crystals in 86% yield, Mp. 210–211°C. IR (KBr) ν cm^{-1} = 3200s (NH), 3050 m, 3000 m (C-H aromatic), 2840w, 2800 m (C-H aliphatic), 1685s (C=O), 1575s (C=N), 1530s, 1480s, 1440s (C-H aromatic), 1300s, 1280s, 1240s, 1190s, 1040s, 975s (C-O, C-H, C-N), 805s, 760s, 725s, 705s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 11.80 (s, 1H, NH*), 7.90–7.20 (m, 9H, aromatic-H), 4.72 (s, 1H, SCH_2), 4.10 (s, 2H, SCH_2). Elemental analysis for $C_{17}H_{14}BrN_3OS$ (388.29); Calcd: C; 52.59, H; 3.63, N; 10.82, S; 8.26%. Found: C; 52.91, H; 3.77, N; 11.00, S; 7.85%.

5.5 *Synthesis of 2-benzyl-1,3-thiazolo[3,2-b]-s-triazoles (15a–l) and 20a–d*



15a–l



20a–d

5.5.1 General procedures. A mixture of 3-benzyl-s-triazole-5(1H)-thiol (**13**) [23] (5 mmol) and aromatic, aliphatic or cyclic ketones (5 mmol) in glacial acetic acid (25 ml) and catalytic amount of concentrated sulfuric acid was refluxed for 3 hours, then after cooling diluted with water and neutralized with ammonia solution, the crude product filtered and washed with water, then crystallized from benzene-cyclohexane to give **15a–l** and **20a–d** as colorless or white needles in 62–81% yield. The Rf values were measured using benzene-ethylacetate mixture as an eluent in ratio (8:2) unless other wise stated.

5.5.2 2-benzyl-5-phenylthiazolo[3,2-b][1,2,4]triazole (15a). R = H, $R_1 = C_6H_5$. This was obtained as colorless crystals in 88% yield, Mp. 67–68 °C, $R_f = 0.68$. IR (KBr) ν cm^{-1} = 3020w (C-H aromatic), 3010w, 2900w (C-H aliphatic), 1590s (C=N), 1540 m, 1460s, 1435s (C-H aromatic), 1420s (C-H aromatic), 1250s, 1070w, 1025s (C-O, C-H, C-N), 740s, 725s, 675s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 8.28–7.11 (m, 10H, aromatic-H), 6.98 (s, 1H, CH), 4.25 (s, 2H, CH_2). MS m/z (%) = 291 [M^+] (100), 290 (69), 174 (22), 173 (5), 134 (50), 129 (11), 117 (23), 116 (15), 102 (14), 91 (47), 77 (16), 65 (8), 51 (6). Elemental analysis for $C_{17}H_{13}N_3S$ (291.38); Calcd: C; 70.08, H; 4.49, N; 14.42, S; 11.00%. Found: C; 70.08, H; 4.65, N; 14.54, S; 10.84%.

5.5.3 2-benzyl-5-(4-chlorophenyl)thiazolo[3,2-b][1,2,4]triazole (15b). R = H, R_1 = *p*-ClC_6H_4. This was obtained as colorless crystals in 76% yield, Mp. 155–156 °C, $R_f = 0.63$. IR (KBr) ν cm^{-1} = 3030s (C-H aromatic), 2950 m, 2920 m (C-H aliphatic), 1605s (C=N), 1575s, 1560s, 1500s, 1465s (C-H aromatic), 1290s, 1280s, 1200s, 1080s, 990s (C-O, C-H, C-N), 820s, 760s, 710s, 695s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 8.10–7.20 (m, 9H, aromatic-H), 7.00 (s, 1H, CH), 4.25 (s, 2H, CH_2). MS m/z (%) = 327 [M^{+2}] (34), 326 [M^{+1}] (83), 325 [M^+] (78), 324 [M^{-1}] (100), 210 (4), 208 (4), 173 (31), 170 (15), 168 (41), 163 (18), 165 (5), 138 (8), 136 (17), 117 (40), 116 (26), 91 (67), 77 (11), 65 (16), 51 (9). Elemental analysis for $C_{17}H_{12}ClN_3S$ (325.82); Calcd: C; 62.66, H; 3.71, N; 12.89, S; 9.84%. Found: C; 62.43, H; 3.92, N; 12.67, S; 9.58%.

5.5.4 2-benzyl-5-(4-bromophenyl)thiazolo[3,2-b][1,2,4]triazole (15c). R = H, R_1 = *p*-BrC_6H_4. This was obtained as colorless crystals in 74% yield, Mp. 167–168 °C, $R_f = 0.65$. IR (KBr) ν cm^{-1} = 3100s (C-H aromatic), 2820 m (C-H aliphatic), 1600s (C=N), 1560s, 1530s, 1490s, 1460s (C-H aromatic), 1315s, 1260s, 1160s, 1000s, 840s (C-O, C-H, C-N), 810s, 750s, 722s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 8.10–7.20 (m, 9H, aromatic-H), 6.95 (s, 1H, CH), 4.25 (s, 2H, CH_2). MS m/z (%) = 371 [M^{+2}] (34), 370 [M^{+1}] (9), 369

[M^+] (36), 368 (5), 214 (7), 212 (6), 209 (4), 207 (5), 182 (15), 180 (9), 173 (20), 117 (29), 116 (40), 91 (100), 77 (55), 65 (32), 51 (57). Elemental analysis for $C_{17}H_{12}BrN_3S$ (370.27); Calcd: C; 55.14, H; 3.26, N; 8.66, S; 9.84%. Found: C; 54.87, H; 3.23, N; 11.25, S; 9.34%.

5.5.5 2-benzyl-5-(4-methylphenyl)thiazolo[3,2-b][1,2,4]triazole (15d). R = H, R_1 = p-$CH_3C_6H_4$. This was obtained as colorless crystals in 74% yield, Mp. 108-109 °C, R_f = 0.68. IR (KBr) ν cm^{-1} = 3100w (C-H aromatic), 2990w, 2900w, (C-H aliphatic), 1600s (C=N), 1580s, 1540s, 1480s, 1420s (C-H aromatic), 1300s, 1250s, 1220s, 1180s, 1030s (C-O, C-H, C-N), 815s, 760s, 735s, 720s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.90–7.20 (m, 9H, aromatic-H), 6.80 (s, 1H, CH), 4.25 (s, 2H, CH_2), 2.40 (s,3H, CH_3). MS m/z (%) = 305 [M^+] (100), 304 [M^{-1}] (30), 188 (6), 148 (27), 143 (15), 117 (28), 116 (35), 91 (70), 77 (26), 65 (36), 51 (17). Elemental analysis for $C_{18}H_{15}N_3S$ (305.4); Calcd: C; 70.79, H; 4.95, N; 13.73, S; 10.49%. Found: C; 70.43, H; 5.11, N; 13.64, S; 10.24%.

5.5.6 2-benzyl-5-(4-methylphenyl)thiazolo[3,2-b][1,2,4]triazole (15e). R = H, R_1 = p-$CH_3OC_6H_4$. This was obtained as colorless crystals in 78% yield, Mp. 94–95 °C, R_f = 0.63. IR (KBr) ν cm^{-1} = 3100w (C-H aromatic), 2980w, 2900w, (C-H aliphatic), 1600s (C=N), 1580s, 1540s, 1480s, 1420s (C-H aromatic), 1290s, 1250s, 1220s, 1180s, 1030s (C-O, C-H, C-N), 820s, 760s, 735s, 720s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 8.00–6.80 (m, 9H, aromatic-H), 6.70 (s, 1H, CH), 4.25 (s, 2H, CH_2), 3.71 (s,3H,OCH_3). Elemental analysis for $C_{18}H_{15}N_3OS$ (321.40); Calcd: C; 67.26, H; 4.70, N; 13.07, S; 9.97%. Found: C; 67.11, H; 4.83, N; 12.97, S; 9.46%.

5.5.7 3-benzyl-5-(4-acetylaminophenyl)thiazolo[3,2-b][1,2,4]triazole (15f). R = H, R_1 = p-$CH_3CONHC_6H_4$. This was obtained as colorless crystals in 71% yield, Mp. 193–195°C, R_f = 0.41, benzene-ethylacetate mixture was used as an eluent in ratio (6:4). IR (KBr) ν cm^{-1} = 3200s (NH), 3050 m (C-H aromatic), 2970 m, 2960 m, 2890 m (C-H aliphatic), 1680s (C=O), 1610s (C=N), 1560s, 1510s, 1480s, 1400s (C-H aromatic), 1360s, 1305s, 1140s, 1020 m (C-O, C-H, C-N), 805s, 740s, 705s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 8.00–7.20 (m, 10H 9H, aromatic-H and 1H, NH), 7.00 (s, 1H, CH), 4.25 (s, 2H, CH_2), 2.20 (s, 3H, CH_3). MS m/z (%) = 348 [M^+] (100%). Elemental analysis for $C_{19}H_{16}N_4OS$ (348.43); Calcd: C; 65.5, H; 4.63, N; 16.08, S; 9.20%. Found: C; 65.24, H; 5.08, N; 15.93, S; 8.86%.

5.5.8 2-benzyl-5-methylthiazolo[3,2-b][1,2,4]triazole (15g). R = H, R_1 = CH_3. This was obtained as colorless crystals in 65% yield, Mp. 70–71°C, R_f = 0.51, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3030s (C-H aromatic), 2970s, 2900s, 2800 m (C-H aliphatic), 1620s (C=N), 1580s, 1550s, 1495s, 1450s, 1430s (C-H aromatic), 1350s, 1250s, 1060s (C-O, C-H, C-N), 730s, 710s, 690s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.40–7.11 (m, 5H, aromatic-H), 6.40 (s, 1H, CH), 4.15 (s, 2H, CH_2), 2.45 (s, 3H, CH_3). Elemental analysis for $C_{12}H_{11}N_3S$ (229.31); Calcd: C; 62.85, H; 4.83, N; 18.32, S; 13.98%. Found: C; 62.57, H; 4.50, N; 8.41, S; 13.55%.

5.5.9 2-benzyl-5,6-dimethylthiazolo[3,2-b][1,2,4]triazole (15h). R = R_1 = CH_3. This was obtained as colorless crystals in 64% yield, Mp. 63–64°C, R_f = 0.5, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3040 m (C-H aromatic), 2970 m, 2960 m (C-H aliphatic), 1600 m (C=N), 1560s, 1470s, 1460s (C-H aromatic),

1350s, 1305s, 1140s, 1020 m (C-O, C-H, C-N), 730s, 705s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) $\delta = 7.50$–7.20 (m, 5H, aromatic-H), 4.15 (s, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.30 (s,3H, CH_3). MS m/z (%) = 243 [M^+] (100%). Elemental analysis for $C_{13}H_{13}N_3S$ (343.33); Calcd: C; 64.17, H; 5.39, N; 17.27, S; 13.18%. Found: C; 63.86, H; 5.40, N; 17.43, S; 12.91%.

5.5.10 2-benzyl-6-ethyl-5-methylthiazolo[3,2-b][1,2,4]triazole (15i). R = C_2H_5, R_1 = CH_3. This was obtained as colorless liquid in 71% yield, $R_f = 0.7$, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3030 m (C-H aromatic), 2900 m, 2850 wm (C-H aliphatic), 1600s (C=N), 1490s, 1485s, 1400 m, (C-H aromatic), 1345s, 1300s, 1140s, 1030 m (C-O, C-H, C-N), 765s, 730s, 700s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) $\delta = 7.51$–7.01 (m, 5H, aromatic-H), 4.15 (s, 2H, CH_2), 2.45 (q, $J = 7$ Hz, 2H, CH_2), 2.21 (s,3H, CH_3), 1.11 (t, $J = 7$ Hz, 3H,CH_3). Elemental analysis for $C_{14}H_{15}N_3S$ (257.36); Calcd: C; 65.34, H; 5.87, N; 16.33, S; 12.46%.

5.5.11 2-benzyl-6-ethyl-5-propylthiazolo[3,2-b][1,2,4]triazole (15j). R = C_2H_5, R_1 = $CH_3(CH_2)_2$-. This was obtained as colorless liquid in 74% yield, $R_f = 0.6$, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3050s (C-H aromatic), 2960 m, 2900s, 2890s (C-H aliphatic), 1600s (C=N), 1490s, 1470s, 1400 m, (C-H aromatic), 1350s, 1310s, 1230s, 1160s, 1030s, 910s (C-O, C-H, C-N), 730s, 700s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) $\delta = 7.50$–7.02 (m, 5H, aromatic-H), 4.15 (s, 2H, CH_2), 2.50 (m, 4H, 2 CH_2), 1.65 (q, 2H, CH_2), 1.00 (t, 3H, CH_3), 0.82 (t,3H,CH_3). Elemental analysis for $C_{16}H_{19}N_3S$ (285.41); Calcd: C; 67.33, H; 6.71, N; 14.72, S; 11.23%.

5.5.12 2-benzyl-6-acetyl-5-methylthiazolo[3,2-b][1,2,4]triazole (15 k). R = COH_3, R_1 = CH_3. This was obtained as colorless crystals in 62% yield, Mp. 102–103°C, $R_f = 0.48$, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3030s (C-H aromatic), 2980 m, 2870 m (C-H aliphatic), 1660 (C=O), 1600 m (C=N), 1560s, 1510s, 1460s, (C-H aromatic), 1350s, 1300s, 1140s, 1050 m (C-O, C-H, C-N), 730s, 700s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) $\delta = 7.30$–7.15 (m, 5H, aromatic-H), 4.13 (s, 2H, CH_2), 2.83 (s,3H, $COCH_3$), 2.50 (s, 3H, CH_3). MS m/z (%) = 271 [M^+] (100%). Elemental analysis for $C_{14}H_{13}N_3S$ (271.34); Calcd: C; 61.97, H; 4.83, N; 15.49, S; 11.82%. Found: C; 61.40, H; 4.93, N; 15.41, S; 11.31%.

5.5.13 (2-benzyl-6-benzoyl-5-methylthiazolo[3,2-b][1,2,4]triazole (15l). R = COC_6H_5, R_1 = CH_3. This was obtained as colorless crystals in 67% yield, Mp. 99–100°C, $R_f = 0.7$, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3010w (C-H aromatic), 2970w, 2890w (C-H aliphatic), 1645 (C=O), 1600w (C=N), 1580s, 1480s, (C-H aromatic), 1350s, 1305s, 1295s, 1140s, 1020 m (C-O, C-H), 720s, 695s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) $\delta = 7.70$–7.00 (m, 10H, aromatic-H), 4.16 (s, 2H, CH_2), 2.60 (s, 3H, CH_3). Elemental analysis for $C_{19}H_{15}N_3S$ (333.41); Calcd: C; 68.45, H; 4.53, N; 12.6, S; 9.62%. Found: C; 68.09, H; 4.37, N; 13.66, S; 9.28%.

5.5.14 2-benzylcyclopentenyl[1′,2′:4,5]-1,3-thiazolo[3,2-b][1,2,4]triazoles (20a). R, R_1 = -$CH_2CH_2CH_2$-. This was obtained as colorless crystals in 68% yield, Mp. 69–70°C, $R_f = 0.32$, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr)

ν cm^{-1} = 3020w (C-H aromatic), 2940w, 2830w (C-H aliphatic), 1600w (C=N), 1500s, 1430s, (C-H aromatic), 1340s, 1320s, 1260 m, 1090s, (C-O, C-H, C-N), 735s, 680s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.40–7.20 (m, 5H, aromatic-H), 4.01 (s, 2H, CH_2), 2.40, (m, 4H, $2CH_2$), 1.71 (m, 2H, CH_2). MS m/z (%) = 255 [M^+] (100%). Elemental analysis for $C_{14}H_{13}N_3S$ (255.34); Calcd: C; 65.85, H; 5.13, N; 16.46, S; 12.56%. Found: C; 65.61, H; 5.40, N; 16.31, S; 12.27%.

5.5.15 2-benzylcyclohexenyl[1′,2′:4,5]-1,3-thiazolo[3,2-b]-s-triazoles (20b). R, R_1 = -$CH_2CH_2CH_2CH_2$-. This was obtained as colorless crystals in 70% yield, Mp. 67–69°C, R_f = 0.58, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3030w (C-H aromatic), 2960s (C-H aliphatic), 1600 m (C=N), 1475s, 1430s, (C-H aromatic), 1325s, 1300s, 1240s, 1060s, 1030 m (C-O, C-H, C-N), 730s, 695s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.40–7.10 (m, 5H, aromatic-H), 4.11 (s, 2H, CH_2), 2.81-2.51 (m, 4H, $2CH_2$), 1.91-1.70 (m, 4H, $2CH_2$). MS m/z (%) = 269 [M^+] (100%). Elemental analysis for $C_{15}H_{15}N_3S$ (269.37); Calcd: C; 66.88, H; 5.61, N; 15.59, S; 11.94%. Found: C; 66.69, H; 5.94, N; 15.48, S; 11.53%.

5.5.16 2-benzylcycloheptenyl[1′,2′:4,5]-1,3-thiazolo[3,2-b]-s-triazoles (20c). R, R_1 = -$CH_2(CH_2)_3CH_2$-. This was obtained as colorless liquid in 81% yield, R_f = 0.64, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3030w (C-H aromatic), 2900s, 2840s (C-H aliphatic), 1590s (C=N), 1490s, 1475s 1450s, 1420 m (C-H aromatic), 1350s, 1305s, 1230s, 1170s, 1020 m (C-O, C-H, C-N), 730s, 695s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.27–7.01 (m, 5H, aromatic-H), 4.01 (s, 2H, CH_2), 2.91 (4H, $2CH_2$), 2.51 (4H, $2CH_2$), 1.65 (m, 2H, CH_2).). MS m/z (%) = 283 [M^+] (100%). Elemental analysis for $C_{16}H_{17}N_3S$ (283.40); Calcd: C; 67.81, H; 6.04, N; 14.83, S; 11.31%.

5.5.17 2-benzylcyclooctenyl[1′,2′:4,5]-1,3-thiazolo[3,2-b]-s-triazoles (20d). R, R_1 = -$CH_2(CH_2)_4CH_2$-. This was obtained as colorless crystals in 76% yield, Mp. 70–71°C, R_f = 0. 0.67, benzene-ethylacetate mixture was used as an eluent in ratio (8:2). IR (KBr) ν cm^{-1} = 3030w (C-H aromatic), 2900s, 2850s (C-H aliphatic), 1600 m (C=N), 1480s, 1475s 1450s, (C-H aromatic), 1340s, 1305s, 1260s, 1070 m, 1020 m (C-O, C-H, C-N), 735s, 695s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.40–7.21 (m, 5H, aromatic-H), 4.20 (s, 2H, CH_2), 3.01-2.70 (t, 4H, $2CH_2$), 1.91 (m, 4H, $2CH_2$), 1.30 (m, 4H, $2CH_2$). MS m/z (%) = 297 [M^+] (100%). Elemental analysis for $C_{17}H_{19}N_3S$ (297.43); Calcd: C; 68.65, H; 6.44, N; 14.13, S; 10.78%. Found: C; 68.89, H; 6.79, N; 14.04, S; 10.42%.

5.6 *Synthesis of thiazolo[3,2-b][1,2,4]triazol 15a–c using poly-phosphoric acid (PPA)*

A sample of the uncyclized ketones **14a–c** (5 mmol) was refluxed in poly phosphoric acid (8 ml) in oil-bath for 3 hours at 130–131°C. The mixture was cooled, neutralized with sodium bicarbonate solution and the crude product thus formed was collected by filtration, washed with water and crystallized from benzene-cyclohexane to give **15a–c** in 54, 51 and 60% yield respectively. The analyses of these compounds were in satisfactorily agreement with those obtained using the acidified acetic acid method.

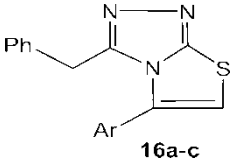
5.7 *Synthesis of thiazolo[3,2-b][1,2,4]triazole 15a using the uncyclized ketone 14a*

Refluxing of 5-benzyl-3-phenylacetylthio-1,2,4-triazole (**14a**) (3 mmol) in glacial acetic acid (25 ml) and catalytic amount of concentrated H_2SO_4 for 3 hours. The reaction mixture was cooled and neutralized by ammonium hydroxide. The precipitate thus formed was collected by filtration, dried and crystallized from cyclohexane to give **15a** in 80% yield. The analytical data were in agreement with the prepared above.

5.8 *Synthesis of 2-phenyl-N′-(4-phenylthiazol-2-yl)acetohydrazide (18)*

A mixture of 1-(2-phenylacetyl)thiosemicarbazide (**17**; 10 mmol) and phenyl bromomethyl ketone (10 mmol) in ethanol (30 ml) was refluxed on a water bath for 3 hours. The mixture was cooled and the solid product thus formed was collected by filtration and crystallized from ethanol to give 2-phenyl-N′-(4-phenylthiazol-2-yl)acetohydrazide (**18**) as white crystals in 89% yield, Mp. 238–239°C. IR (KBr) ν cm^{-1} = 3150s (NH), 3030s (C-H aromatic), 2970s, 2850 m (C-H aliphatic), 1680s (C=O), 1615s (C=N), 1590s, 1500s, 1475s 1450s, (C-H aromatic), 1340s, 1305s, 1260s, 1050s, 1020 m (C-O, C-H, C-N), 735s, 710s (aromatic). ^{1}HNMR ($DMSO_{d6}$, 90 MHz) δ = 10.90 (s, 1H, NH), 7.61–7.10 (m, 12H {11H, aromatic-H, 1H, NH and C5-H}), 3.40 (s, 2H, CH_2). MS m/z (%) = 309 [M^+] (78%). Elemental analysis for $C_{17}H_{15}N_3OS$ (309.39); Calcd: C; 66.00, H; 4.89, N; 13.58, S; 10.36. Found: C; 65.73, H, 4.80, N; 13.82, S; 10.01.

5.9 *Synthesis of 5-aryl-3-benzyl-1,3-thiazolo[2,3-c]-s-triazoles (16a–c)*



16a-c

5.9.1 Method (A): 3-benzyl-5-phenylthiazolo[2,3-c][1,2,4]triazole (16a). A mixture of **18** (3 mmol) was refluxed with $POCl_3$ (10 ml) in an oil-bath at 130°C for 3 hours. The reaction mixture was cooled and neutralized with aqueous sodium carbonate, the precipitated product was filtered, washed with water and crystallized from benzene to give **16a**, as colorless needles in 64% yield, Mp. 124–125°C. IR (KBr) ν cm^{-1} = 3020w (C-H aromatic), 2900w (C-H aliphatic), 1615 m (C=N), 1550s 1500 m, 1435 m, 1420s (C-H aromatic), 1350s, 1250s, 1090w, 1040s (C-O, C-H, C-N), 740s, 720s, 695s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.72 (t, J = 1.5 Hz, 2H, aromatic-H), 7.28 (m, 8H, aromatic-H), 6.82 (s, 1H, CH), 3.85 (s, 2H, CH_2). MS m/z (%) = 291 [M^+] (100%), Elemental analysis for $C_{17}H_{13}N_3S$ (291.38). Calcd: C; 70.07, H; 4.49, N; 14.42, S; 11.00. Found: C; 70.18, H; 4.60, N; 14.62, S; 10.73.

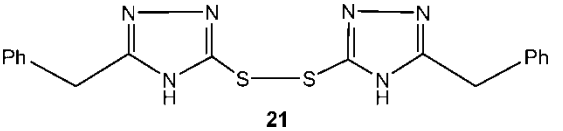
5.9.2 Method (B). A mixture of uncyclized ketones **14a–c** (3 mmol) were refluxed with $POCl_3$ (10 ml) and anhydrous xylene (50 ml) on oil-bath at 130°C for 10 hours. The reaction solvent was removed and the residue washed with sodium bicarbonate solution (30%), the solid products thus obtained were collected by filtration and crystallized from benzene-cyclohexane

to give **16a–c** as colorless or white needles in 46-61% yield. Analytical data of compound **16a** (46%) was in satisfactorily agreement with the one obtained as described in Method A.

5.9.3 3-benzyl-5-(4-chlorophenyl)thiazolo[2,3-c][1,2,4]triazole (16b). Ar = *p*-ClC_6H_4. This was obtained as colorless crystals in 61% yield, Mp. 191–192°C. IR (KBr) ν cm^{-1} = 3020s (C-H aromatic), 2950w (C-H aliphatic), 1595s (C=N), 1560s 1480s, 1460 m, 1415s (C-H aromatic), 1340 m, 1260 m, 1160s, 1080s, 1015s, 930s (C-O, C-H, C-N), 800s, 750s, 720s, 690s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.40–6.50 (m, 9H, aromatic-H), 6.77 (s, 1H, CH), 4.05 (s, 2H, CH_2). MS m/z (%) = 327 [M^{+2}] (35%), 327 [M^{+1}] (85%), 327 [M^+] (70%). Elemental analysis for $C_{17}H_{12}ClN_3S$ (325.82); Calcd: C; 62.66, H; 3.71, N; 12.89, S; 9.84%. Found: C; 62.83, H; 3.82, N; 12.65, S; 9.49%.

5.9.4 3-benzyl-5-(4-bromophenyl)thiazolo[2,3-c][1,2,4]triazole (16c). Ar = *p*-BrC_6H_4. This was obtained as colorless crystals in 56% yield, Mp. 155–157°C. IR (KBr) ν cm^{-1} = 3020s (C-H aromatic), 2950w (C-H aliphatic), 1595s (C=N), 1560s 1480s, 1460 m, 1415s (C-H aromatic), 1340 m, 1260 m, 1160s, 1080s, 1015s, 930s (C-O, C-H, C-N), 800s, 750s, 720s, 690s (aromatic). ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.70–6.53 (m, 9H, aromatic-H), 6.99 (s, 1H, CH), 4.10 (s, 2H, CH_2). MS m/z (%) = 327 [M^{+2}] (35%), 327 [M^{+1}] (20%), 327 [M^+] (65%). Elemental analysis for $C_{17}H_{12}BrN_3S$ (370.27); Calcd: C; 55.14, H; 3.26, N; 11.34, S; 8.66%. Found: C; 54.86, H; 3.51, N; 11.39, S; 8.21%.

5.10 *Synthesis of bis-(5-benzyl-1,2,4-triazol-3-yl)disulphide (21)*



21

A sample of 3-benzyl-s-triazole-5(1H)-thiol (**13**; 10 mole) in glacial acetic acid (30 ml) was refluxed in the presence of concentrated H_2SO_4 for 3 hours. The reaction mixture was then cooled and neutralized with ammonia solution the precipitate thus formed was collected by filtration, washed with water and crystallized from ethanol to give the disulphide derivative **21** as white needles crystals in 81% yield, Mp. 184–185°C, Lit. 184°C [58]. IR (KBr) ν = 3150 m, 3020 m, 2910 m, 2700 m, 1600 m, 1575s, 1490s, 1440s, 1060s, 730s, 720s cm^{-1}. ($CDCl_3$, 90 MHz) δ = δ 7.20–7.01 (m, 10H, aromatic protons), 4.01 (s, 4H, 2CH2). MS m/z (%) = 380 M^+ (22.2%). Elemental analysis for $C_{18}H_{16}N_6S_2$ (380.49). Calcd: C; 56.82, H; 4.24, N; 22.08, S; 16.85%. Found: C; 57.12, H; 4.57, N; 21.81, S; 16.54%.

5.11 *Synthesis of thiazolo[3,2-b][1,2,4]triazoles 15c–e using the disulphide 21*

A mixture of disulphide **21** (4 mmol) and appropriate aromatic ketone such as *p*-bromo, *p*-methyl or *p*-methoxyacetophenone (4 mmol) in glacial acetic acid (25 ml) and catalytic amount of concentrated H_2SO_4 was refluxed for 3 hours. The reaction mixture was then cooled and neutralized with ammonia solution, the precipitate thus formed was collected by filtration, washed with water and crystallized from cyclohexane to give **15c** (66%), **15d** (78%)

and **15e** (71%) yields, respectively. The analyses of **15c–e** were in satisfactory agreement with those obtained in this text.

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