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Heterocyclization of 1-aryl/alkyl-2-thiobiureas to 4-aryl/alkyl-3-substituted-Δ^2-1,2,4-triazolin-5-ones

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Abstract—Synthesis of a range of 1,2,4-triazolin-5-ones has been carried out by thermally induced cyclization of 1-aryl/alkyl-2-alkyl isothiobiureas **4**. The required isothiobiureas were generated in situ by the reaction of alkyl halides with 1-aryl/alkyl-2-thiobiureas **3** in acidic medium at reflux. The reaction proceeds after *S*-alkylation of the thiobiureas and is demonstrated by the isolation of the alkyl isothiobiurea intermediates and their subsequent acid catalyzed thermal cyclization.

The cyclization of compounds having an extended urea-like chain of more than five atoms has been shown to be an excellent method for the synthesis of several heterocycles like 1,3,4-thiodiazoles, 1,2,4-triazoles and 1,3,5-triazines. 1-Substituted benzoyl thiosemicarbazide on irradiation with microwaves in aqueous alkali is reported to form 3-aryl-1,2,4-triazoline-5-thiones.[1] Cyclization of 1,4-disubstituted thiosemicarbazides can be effected in acidic and alkaline media.[2] For instance, 1-phenylacetyl-4-substituted thiosemicarbazide in alkaline and acidic media undergoes cyclization to yield 3-benzyl-Δ^2-1,2,4-triazoline-5-thiones and 2-amino-5-benzyl-1,3,4-thiodiazoles, respectively. But 2,4-disubstituted thiosemicarbazides on reaction with acetone in an acidic medium afford 1,2,4-triazolidine-3-thione derivatives.[3] The acid catalyzed cyclization of 1-arylamidino thiosemicarbazide affords 3-arylamino-Δ^2-1,2,4-triazoline-5-thione.[4] On the other hand, the cyclization[5] and the phase transfer catalyzed cyclization[6] of 1-acyl bithiobiurea resulted in the formation of 1,2,4-triazole,[5] 1,3,4-thiodiazole[5] and 1,2,4-triazoline-3-thione[6] derivatives. It has been reported that 1,3-diamino urea[7] and thiourea[8] on heating with carboxylic acids afford 4-amino-3-substituted-Δ^2-1,2,4-triazolin-5-one and 5-substituted amino mercapto-1,2,4-triazole, respectively. Depending upon the reaction conditions, 1[9]- and 1,6-[4,10,11] substituted-2,5-dithiobiureas on heating yielded triazoline-5-thiones[9] and 1,3,4- thiodiazole[4,10,11] derivatives. The chemistry of 1-substituted thiobiurea remains almost unexplored and hence our studies were mainly aimed at exploring the versatility of 1-substituted-2-thiobiureas, which could be considered as a 1,4-disubstituted thiosemicarbazide, in the preparation of 1,2,4-triazolin-5-one.

1. Results and discussion

The reaction of semicarbazide hydrochloride **1** with an aryl/alkyl isothiocyanate **2** in the presence of anhydrous sodium acetate in dry acetonitrile was found to afford a product in reasonably good yields. Spectroscopic analysis indicated it to be a condensation product, e.g. 1-aryl/alkyl-2-thiobiurea **3**. Though the semicarbazide contains three nitrogens, the condensation would occur only on N-1 as it alone is basic in nature (Scheme 1). Compounds **3**(**a**–**i**) prepared similarly by the condensation of isothiocyanates with semicarbazide are listed below (Table 1, entries 1–9).

The reaction of 1-phenyl-2-thiobiurea **3a** with butyl iodide in dry ethanol containing a trace amount of hydroiodic acid at reflux temperature was found to afford a product with molecular composition $C_{12}H_{15}N_3OS$. Even though the presence of sulfur was detected, the compound did not undergo dehydrosulfurization with hot sodium plumbite solution indicating the absence of any –NH–C(=S)–NH or =N–C(=S)–NH_2 grouping. The dissolution of the product in dilute sodium hydroxide solution showed that it has in all probability an enolisable carbonyl group. From the molecular composition it could be inferred that after S-butylation, the intermediate product underwent eliminative cyclization yielding 4-phenyl-3-butylthio-Δ^2-1,2,4-triazolin-5-one **5a**. It is corroborated by the fact that **4a** formed on reaction of **3a** with butyl iodide in alkaline medium undergoes cyclization on treating with acid even at room temperature. The S-alkylated intermediate **4** formed can undergo cyclization in five different ways (Scheme 2).

If the nitrogen atom in the 1-position of the thiobiurea makes a nucleophilic attack on the carbonyl carbon, displacing ammonia the product formed would be 4-aryl/alkyl-3-alkylthio-Δ^2-1,2,4-triazolin-5-one **5** (path a) whereas if water is eliminated, the product formed would

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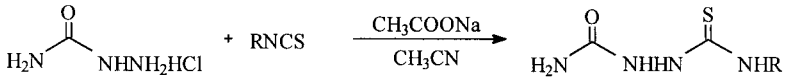

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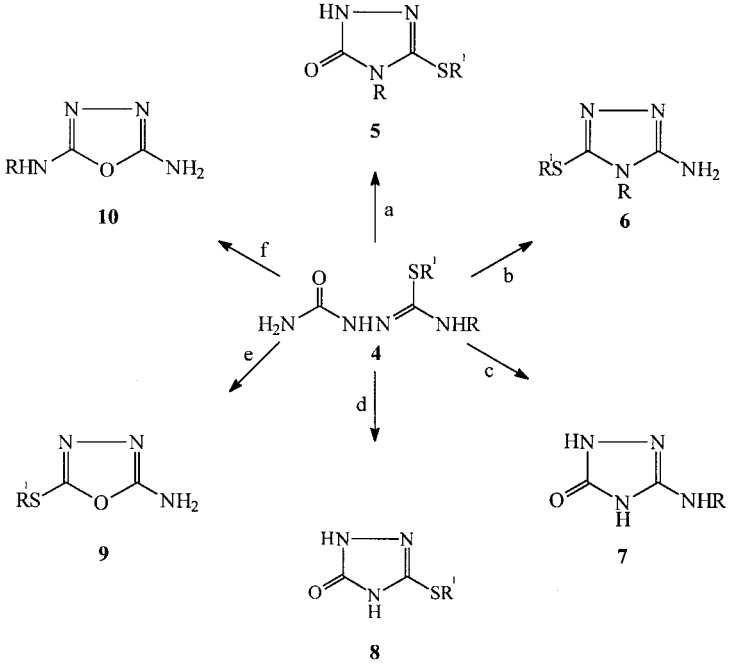
Scheme 1. R: a=Ph; b=*p*-MeC_6H_4; c=*p*-$MeOC_6H_4$; d=*p*-ClC_6H_4; e=*p*-$EtOC_6H_4$; f=Me; g=Et; h=Pr; i=Bu.

Table 1. 1-Aryl/alkyl-2-thiobiureas

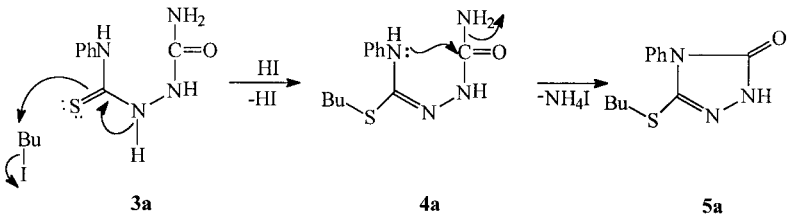
Entry	R	Product (yield, %)
1	C_6H_5	**3a** (72)
2	*p*-MeC_6H_4	**3b** (74)
3	*p*-$MeOC_6H_4$	**3c** (70)
4	*p*-$EtOC_6H_4$	**3d** (74)
5	*p*-ClC_6H_4	**3e** (78)
6	Me	**3f** (62)
7	Et	**3g** (65)
8	Pr	**3h** (64)
9	Bu	**3i** (62)

be 3-amino-4-aryl/alkyl-5-alkylthio-1,2,4-triazole **6** (path b). On the other hand, if the nitrogen atom at 6-position displaces alkyl mercaptan or aryl/alkyl amine the product formed would be 3-aryl/alkyl amino-Δ^2-1,2,4-triazolin-5-one **7** (path c) or 3-alkylthio-Δ^2-1,2,4-triazolin-5-one **8** (path d). The formation of **7** and **8** can be ruled out as N6 being adjacent to a carbonyl group is electrophilic in nature. 2-Amino-5-alkylthio-1,3,4-oxadiazole **9** (path e) or 2-amino-5-aryl/alkyl amino-1,3,4-oxadiazole **10** (path f) would be formed if the oxygen atom of the carbonyl group at the 5-position displaces aryl/alkyl amine or mercaptan.

When **3a** is heated with butyl iodide in dry ethanol containing hydroiodic acid, ammonium iodide was found to be present along with **5a**. This indicated that S-alkylated product underwent cyclization only by path a. The carbonyl carbon is electrophilic in nature and hence the displacement of the NH_2 group attached to the carbonyl carbon occurs by the intramolecular nucleophilic attack of the nitrogen atom at position 1 (Scheme 3, mechanism). It is observed that addition of acid facilitates the reaction due to a shift in equilibrium towards the product by rapid expulsion of



Scheme 2. R^1=Bu, Bn, Me, allyl.



3a 4a 5a

Scheme 3.

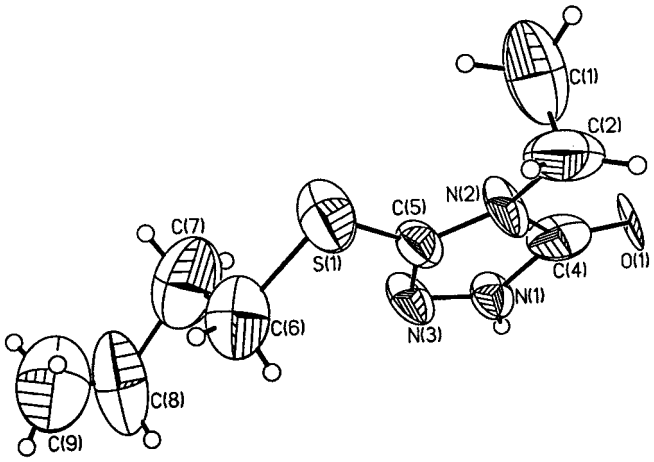


Figure 1. The ORTEP diagram of 4-ethyl-3-butylthio -Δ^2-1,2,4-triazolin-5-one.

Table 2. 1-Aryl-2-S substituted isothiobiurea

Entry	R	R^1	Time (h)	Product (yield, %)
1	C_6H_5	Bu	11	**4a** (60)
2	C_6H_5	Bn	6	**4b** (85)
3	*p*-ClC_6H_4	Bn	5	**4c** (85)
4	*p*-MeC_6H_4	Me	8	**4d** (65)
5	*p*-$MeOC_6H_4$	Me	7	**4e** (70)

Table 3. 4-Aryl/alkyl-3-substitued thio-Δ^2-1,2,4-triazolin-5-ones

Entry	R	R^1	Time (h)	Product (yield, %)
1	C_6H_5	Bu	5	**5a** (82)
2	Me	Bu	5	**5b** (70)
3	Et	Bu	5	**5c** (75)
4	*p*-ClC_6H_4	Bn	4	**5d** (85)
5	Pr	Bn	4	**5e** (82)
6	Bu	Bn	4	**5f** (83)
7	*p*-MeC_6H_4	Me	8	**5g** (88)
8	*p*-$MeOC_6H_4$	Me	8	**5h** (75)
9	Et	Me	8	**5i** (68)
10	*p*-MeC_6H_4	Allyl	11	**5j** (68)
11	*p*-$MeOC_6H_4$	Allyl	11	**5k** (70)
12	*p*-$EtOC_6H_4$	Allyl	11	**5l** (75)

ammonia. No cyclization occurs when the S-alkyl derivative is heated alone, which again indicates that the acid generated in situ or added is a must for the cyclization reaction (Fig. 1).

Compounds **3**(**a**–**c**) similarly, when treated with methyl iodide, benzyl chloride or allyl chloride afforded the S-alkylated isothiobiureas (Table 2, entries 1–5) and triazolin-5-one derivatives (Table 3, entries 1–12). To conclude, a new and simple synthetic strategy for the preparation of Δ^2-1,2,4-triazolin-5-ones from extended urea like chain compounds have been developed.

2. Experimental

Melting points are uncorrected. Infrared spectra were taken on a Perkin–Elmer RX_1 spectrophotometer using KBr pellets, ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 on BRUKER-200, BRUKER-300, JEOLX-90 MHz spectrometers with tetramethylsilane as the internal standard. Mass spectra were recorded at 70 eV ionising voltage on a Jeol-D300 MS instrument. The elemental analyses were performed by the National Chemical Laboratory, Pune. The crystal structure of **5c** was determined on an Enraf-Nonius CAD4 diffractometer with Mo-Kα radiation. All the isothiocyanates were prepared according to the literature procedure.[12]

2.1. General procedure for compounds 3(a–e)

Phenyl isothiocyanate (13.5 ml, 0.1 mol) was added dropwise to a suspension of semicarbazide hydrochloride (11.15 g, 0.1 mol) and anhydrous sodium acetate (8.2 g, 0.1 mol) in acetonitrile (15 ml) and stirred until the pungent smell of the isothiocyanate vanished. The completion of the reaction was confirmed by the absence of any oily layer due to unreacted isothiocyanate, on pouring a portion of the reaction mixture into dilute NaOH. The solid material formed during the reaction was collected and triturated with NaOH (2 M, 20 ml). Decolourization of the alkaline filtrate with charcoal and neutralization with HCl (10 ml) yielded **3a**. It was collected and crystallized from EtOH/DMF (3:1) mixture.

2.1.1. 1-Phenyl-2-thiobiurea (3a). White solid, mp 218°C; (Found: C, 45.84; H, 4.85; N, 26.43; S, 15.28. $C_8H_{10}N_4OS$ requires C, 45.71; H, 4.76; N, 26.67; S, 15.24%); R_f (10% $CHCl_3$/isopropanol) 0.47; ν_{max} (KBr, pellet) 3510, 3500, 3450, 3380, 3000, 1690, 1510, 1320 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 5.87 (s, 1H, N*H*), 6.03 (s, 1H, N*H*), 6.05–6.6 (br s, 2H, NH_2), 6.72 (s, 1H, N*H*), 6.9–7.1 (m, 5H, Ph); δ_C (90 MHz, DMSO-d_6) 118.3, 121.7, 127.9, 138.1, 154.8, 160.1; *m*/*z* 210 (M^+, 35), 151 (24), 135 (38), 91 (100).

The other 1-aryl-2-thiobiureas **3**(**b**–**e**) similarly prepared by the condensation of corresponding isothiocyanates with semicarbazides are listed below.

2.1.2. 1-*p*-Tolyl-2-thiobiurea (3b). White solid, mp 192°C; (Found: C, 48.11; H, 5.58; N, 24.93; S, 14.31. $C_9H_{12}N_4OS$ requires C, 48.21; H, 5.36; N, 25.0; S, 14.29%); R_f (15% $CHCl_3$/isopropanol) 0.47; ν_{max} (KBr, pellet) 3510, 3500, 3450, 3360, 3020, 2950, 1690, 1510, 1320 cm^{-1}; δ_H

(90 MHz, DMSO-d_6) 2.4 (s, 3H, Ar*Me*), 5.85 (s, 1H, N*H*), 6.04 (s, 1H, N*H*), 6.05–6.81 (br s, 2H, NH_2), 7.0 (s, 1H, N*H*), 7.15 (d, *J*=8.7 Hz, 2H, Ph), 7.25 (d, *J*=8.7 Hz, 2H, Ph); δ_C (90 MHz, DMSO-d_6) 30.9, 126.6, 129.5, 130.1, 139.3, 154.8, 162.3; *m/z* 224 (M^+, 100), 165 (18), 149 (21), 105 (88).

2.1.3. 1-*p*-Anisyl-2-thiobiurea (3c). White solid, mp 204°C; (Found: C, 45.08; H, 5.10; N, 23.28; S, 13.53. $C_9H_{12}N_4O_2S$ requires C, 45.0; H, 5.0; N, 23.33; S, 13.33%); R_f (15% $CHCl_3$/isopropanol) 0.49; ν_{max} (KBr, pellet) 3510, 3500, 3460, 3340, 3000, 2930, 1690, 1520, 1320 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 3.8 (s, 3H, ArO*Me*), 5.69 (s, 1H, N*H*), 6.01 (s, 1H, N*H*), 6.05–6.74 (br s, 2H, NH_2), 6.9 (s, 1H, N*H*), 7.08 (d, *J*=8.9 Hz, 2H, Ph), 7.3 (d, *J*=8.9 Hz, 2H, Ph); δ_C (90 MHz, DMSO-d_6) 55.5, 114.8, 124.8, 128.2, 155.1, 160.0, 161.8; *m/z* 240 (M^+, 100), 167 (20), 165 (41), 121 (82).

2.1.4. 1-*p*-Phenetyl-2-thiobiurea (3d). White solid, mp 210°C; (Found: C, 47.36; H, 5.62; N, 22.0; S, 12.67. $C_{10}H_{14}N_4O_2S$ requires C, 47.24; H, 5.51; N, 22.05; S, 12.60%); R_f (20% $CHCl_3$/isopropanol) 0.51; ν_{max} (KBr, pellet) 3520, 3480, 3460, 3340, 3010, 2950, 1680, 1320 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 1.33 (t, *J*=7.3 Hz, 3H, *Me*), 4.1 (q, *J*=7.3 Hz, 2H, ArOCH_2), 5.5 (s, 1H, N*H*), 5.85 (s, 1H, N*H*), 6.01–6.8 (br s, 2H, NH_2), 6.9 (s, 1H, N*H*), 7.0 (d, *J*=9.0 Hz, 2H, Ph), 7.3 (d, *J*=9.0 Hz, 2H, Ph); δ_C (90 MHz, DMSO-d_6) 14.7, 63.8, 115.3, 124.6, 128.2, 154.7, 159.4, 160.4; *m/z* 254 (M^+, 35), 181 (29), 179 (18), 135 (100).

2.1.5. 1-*p*-Chlorophenyl-2-thiobiurea (3e). White solid, mp 188°C; (Found: C, 39.32; H, 3.85; N, 22.96; S, 13.15. $C_8H_9N_4OSCl$ requires C, 39.26; H, 3.68; N, 22.9; S, 13.09%); R_f (30% $CHCl_3$/isopropanol) 0.45; ν_{max} (KBr, pellet) 3520, 3480, 3460, 3340, 3080, 1680, 1340 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 5.73 (s, 1H, N*H*), 5.92 (s, 1H, N*H*), 6.01 (s, 1H, N*H*), 6.06–7.1 (br s, 2H, NH_2), 7.37 (d, *J*=8.6 Hz, 2H, Ph), 7.5 (d, *J*=8.6 Hz, 2H, Ph); δ_C (90 MHz, DMSO-d_6) 127.3, 129.1, 130.5, 133.9, 154.8, 160.8; *m/z* 244.5 (M^+, absent), 172 (11), 170 (44), 126 (100).

2.2. General procedure for compounds 3(f–i)

A solution of semicarbazide hydrochloride (11.15 g, 0.1 mol) in minimum amount of water was warmed with an ethanolic solution of methyl isothiocyanate (7.3 ml, 0.1 mol) in the presence of sodium carbonate (5.3 g, 0.05 mol) for 10 min. The white solid obtained was purified by dissolution in NaOH (2 M, 15 ml). The alkaline solution was decolourised with charcoal and the clear solution was neutralized with HCl (4 ml) to obtain **3f**. It was collected and crystallized from hot ethanol.

2.2.1. 1-Methyl-2-thiobiurea (3f). White needles, mp 212°C; (Found: C, 24.54; H, 5.56; N, 37.86; S, 21.68. $C_3H_8N_4OS$ requires C, 24.32; H, 5.41; N, 37.84; S, 21.62%); R_f ($CHCl_3$) 0.54; ν_{max} (KBr, pellet) 3480, 3450, 3300, 3220, 2950, 1690, 1340 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 3.2 (s, 3H, *Me*), 5.62 (s, 1H, N*H*), 5.7 (s, 1H, N*H*), 6.01 (s, 1H, N*H*), 6.04–6.09 (br s, 2H, NH_2); δ_C (90 MHz, DMSO-d_6) 27.3, 157.8, 160.1; *m/z* 148 (M^+, 100), 132 (21), 89 (14), 73 (6).

The other 1-alkyl-2-thiobiureas **3(g–i)** similarly prepared by the condensation of corresponding isothiocyanates with semicarbazides are listed below.

2.2.2. 1-Ethyl-2-thiobiurea (3g). White needles, mp 202°C; (Found: C, 29.48; H, 6.02; N, 34.52; S, 19.70. $C_4H_{10}N_4OS$ requires C, 29.63; H, 6.17; N, 34.57; S, 19.75%); R_f ($CHCl_3$) 0.48; ν_{max} (KBr, pellet) 3480, 3450, 3300, 3220, 2890, 1670, 1320 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 1.27 (t, *J*=7.3 Hz, 3H, *Me*), 3.65 (q, *J*=7.3 Hz, 2H, CH_2), 5.48 (s, 1H, N*H*), 5.61 (s, 1H, N*H*), 5.9 (s, 1H, N*H*), 6.03–6.08 (br s, 2H, NH_2); δ_C (90 MHz, DMSO-d_6) 14.1, 36.5, 157.6, 160.1; *m/z* 162 (M^+, 100), 146 (18), 118 (13), 88 (3).

2.2.3. 1-Propyl-2-thiobiurea (3h). White needles, mp 212°C; (Found: C, 34.0; H, 6.72; N, 31.86; S, 18.21. $C_5H_{12}N_4OS$ requires C, 34.09; H, 6.82; N, 31.82; S, 18.18%); R_f ($CHCl_3$) 0.47; ν_{max} (KBr, pellet) 3460, 3450, 3300, 3280, 2980, 1690, 1320 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 0.88 (t, *J*=7.1 Hz, 3H, *Me*), 1.64 (m, 2H, CH_2Me), 3.46 (t, *J*=6.9 Hz, 2H, NCH_2), 5.48 (s, 1H, N*H*), 5.62 (s, 1H, N*H*), 5.7 (s, 1H, N*H*), 6.01–6.08 (br s, 2H, NH_2); δ_C (90 MHz, DMSO-d_6) 10.9, 22.1, 38.5, 157.2, 159.8; *m/z* 176 (M^+, 100), 160 (12), 132 (31), 117 (24), 102 (11).

2.2.4. 1-Butyl-2-thiobiurea (3i). White needles, mp 198°C; (Found: C, 37.78; H, 7.3; N, 29.28; S, 16.91. $C_6H_{14}N_4OS$ requires C, 37.89; H, 7.37; N, 29.47; S, 16.84%); R_f ($CHCl_3$) 0.44; ν_{max} (KBr, pellet) 3460, 3450, 3320, 3280, 2950, 1700, 1320 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 0.9 (t, *J*=7.1 Hz, 3H, *Me*), 1.31 (m, 2H, CH_2CH_2Me), 1.52, (m, 2H, CH_2CH_2Me), 3.48 (t, *J*=6.9 Hz, 2H, NCH_2), 5.9 (s, 1H, N*H*), 6.01 (s, 1H, N*H*), 6.04 (s, 1H, N*H*), 6.06–6.1 (brs, 2H, NH_2); δ_C (90 MHz, DMSO-d_6) 13.5, 19.7, 30.7, 40.1, 157.3, 160.2; *m/z* 190 (M^+, 100), 131 (18), 119 (11).

2.3. General procedure for compounds 4(a–e).

To a solution of 1-phenyl-2-thiobiurea **3a** (2.10 g, 0.01 mol) in minimum quantity of NaOH (2 M, 8 ml) in ethanol (20 ml), butyl iodide (1.2 ml, 0.01 mol) was added dropwise and the mixture kept stirred at 20°C for 11 h. The white solid which got precipitated was collected and washed with dilute alkali, to free it from any thiobiurea present, and finally with cold water. Crystallization from DMF/H_2O mixture (1:1) in the cold condition afforded **4a**. The S-benzyl derivatives were formed when an alkaline solution of the 1-aryl-2-thiobiureas were stirred with equivalent quantity of benzyl chloride **4(b–c)**. The S-methylisothiobiurea was obtained by the reaction of an alkaline solution of 1-aryl-2-thiobiurea with equivalent quantity of dimethyl sulfate **4(d–e)**.

2.3.1. 1-Phenyl-2-S-butyl-isothiobiurea (4a). White needles, mp 162°C; (Found: C, 54.11; H, 6.67; N, 18.10; S, 12.08. $C_{12}H_{18}N_4OS$ requires C, 54.13; H, 6.77; N, 21.05; S, 12.03%); R_f (30% Petroleum ether/ethylacetate) 0.51; ν_{max} (KBr, pellet) 3400, 3200, 3150, 3050, 2950, 1670, 1540, 740 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 0.9 (t, *J*=7.4 Hz, 3H, *Me*), 1.4 (m, 2H, CH_2CH_2Me), 1.6 (m, 2H, CH_2CH_2Me), 3.2 (t, *J*=7.2 Hz, 2H, SCH_2), 5.8–6.1 (br s,

2H, NH_2), 8.1 (s, 1H, N*H*), 8.6 (s, 1H, N*H*), 7.3–7.5 (m, 5H, Ph); δ_C (90 MHz, DMSO-d_6) 13.4, 21.8, 30.8, 31.1, 126.8, 129.1, 129.4, 132.3, 145.3, 154.8; *m/z* 266 (M^+, 35), 238 (15), 207 (38), 189 (41), 91 (100).

2.3.2. 1-Phenyl-2-S-benzyl-isothiobiurea (4b). White needles, mp 142°C; (Found: C, 60.18; H, 5.28; N, 18.68 S, 10.71. $C_{15}H_{16}N_4OS$ requires C, 60.0; H, 5.33; N, 18.67; S, 10.67%); R_f (40% Petroleum ether/ethylacetate) 0.42; ν_{max} (KBr, pellet) 3400, 3300, 3150, 3050, 2900, 1670, 1570, 730 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 4.1 (s, 2H, SCH_2), 5.9–6.1 (br s, 2H, NH_2), 7.7 (s, 1H, N*H*), 9.0 (s, 1H, N*H*), 6.9–7.4 (m, 10H, Ph); δ_C (90 MHz, DMSO-d_6) 35.9, 124.3, 126.8, 127.8, 128.7, 129.1, 129.5,132.2, 135.8, 144.8, 155.6; *m/z* 300 (M^+, 11), 209 (22), 135 (28), 91 (100).

2.3.3. 1-*p*-Chlorophenyl-2-S-benzyl isothiobiurea (4c). White needles; mp 154°C; (Found: C, 53.93; H, 4.25; N, 16.85; S, 9.71. $C_{15}H_{15}N_4OSCl$ requires C, 53.81; H, 4.48; N, 16.74; S, 9.57%); R_f (45% Petroleum ether/ethylacetate) 0.41; ν_{max} (KBr, pellet) 3400, 3300, 3150, 3050, 2950, 1670, 1570, 840, 720 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 4.0 (s, 2H, SCH_2), 5.9–6.2 (br s, 2H, NH_2), 8.0 (s, 1H, N*H*), 8.5 (s, 1H, N*H*), 6.8–7.5 (m, 9H, Ph); δ_C (90 MHz, DMSO-d_6) 35.1, 126.7, 127.2, 127.5, 127.8, 128.3, 130.01, 133.1, 133.9, 142.2, 154.5; *m/z* 334.5 (M^+, absent), 276 (11), 244 (33), 211 (100), 170 (43).

2.3.4. 1-*p*-Tolyl-2-S-methyl isothiobiurea (4d). White needles; mp 174°C; (Found: C, 50.41; H, 5.81; N, 23.52; S, 13.55. $C_{10}H_{14}N_4OS$ requires C, 50.42; H, 5.88; N, 23.53; S, 13.45%); R_f (40% Petroleum ether/ethylacetate) 0.47; ν_{max} (KBr, pellet) 3450, 3250, 3180, 3050, 2980, 1600, 1560, 820 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 2.4 (s, 3H, S*Me*), 2.5 (s, 3H *Me*C_6H_4), 6.1–6.2 (br s, 2H, NH_2), 8.4 (s, 1H, N*H*), 9.6 (s, 1H, N*H*), 7.4 (d, *J*=8.7 Hz, 2H, Ph), 7.6 (d, *J*=8.7 Hz, 2H, Ph); δ_C (90 MHz, DMSO-d_6) 14.1, 21.6, 128.1, 130.4, 130.8, 133.4, 146.8, 155.1; *m/z* 238 (M^+, 10), 190 (100), 179 (27), 138 (52).

2.3.5. 1-*p*-Anisyl-2-S-methyl isothiobiurea (4e). White needles, mp 198°C; (Found: C, 47.18; H, 5.52; N, 22.08; S, 12.61. $C_{10}H_{14}N_4O_2S$ requires C, 47.24; H, 5.51; N, 22.04; S, 12.59. Found: C, 47.18; H, 5.52; N, 22.08; S, 12.61%); R_f (40% Petroleum ether/ethylacetate) 0.48; ν_{max} (KBr, pellet) 3450, 3300, 3250, 3150, 2900, 1670, 1570, 840 cm^{-1}; δ_H (90 MHz, DMSO-d_6) 2.4 (s, 3H, S*Me*), 3.7 (s, 3H, O*Me*), 6.4–6.6 (br s, 2H, NH_2), 7.9 (s, 1H, N*H*), 8.7 (s, 1H, N*H*), 6.8 (d, *J*=8.9 Hz, 2H, Ph), 7.1 (d, *J*=8.9 Hz, 2H, Ph); δ_C (90 MHz, DMSO-d_6) 13.9, 55.5, 113.8, 124.9, 128.2, 147.2, 154.1, 160.0; *m/z* 254 (M^+, 21), 226 (38), 206 (100), 195 (13), 166 (66).

2.4. General procedure for the synthesis of 5(a–c)

To a suspension of 1-phenyl-2-thiobiurea **3a** (2.1 g, 0.01 mol) in ethanol (10 ml) containing concentrated hydriodic acid (0.5 ml), BuI (1.2 ml, 0.01 mol) was added and refluxed for 5 h. The solvent was removed by distillation under reduced pressure. The sticky residue was treated with dilute NaOH (2 M, 10 ml). The alkaline extract was decolourised with charcoal and then neutralized with hydrochloric acid (8 ml). The precipitate was collected, dried and then chromatographed on a column of silica gel using petroleum ether/ethyl acetate mixture (80:20) as eluant. The eluate on removal of the solvent yielded **5a**.

2.4.1. 4-Phenyl-3-butylthio-Δ^2-1,2,4-triazolin-5-one (5a). White needles, mp 143°C; (Found: C, 57.97; H, 6.11; N, 16.88; S, 12.87. $C_{12}H_{15}N_3OS$ requires C, 57.83; H, 6.02; N, 16.87; S, 12.85%); R_f (20% petroleum ether/ethyl acetate) 0.44; ν_{max} (KBr, pellet) 3200, 3050, 2950, 1700, 1510, 700 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.9 (t, *J*=7.4 Hz, 3H, *Me*), 1.4 (m, 2H, CH_2CH_2Me), 1.68 (m, 2H, CH_2CH_2Me), 2.9 (t, *J*=7.2 Hz, 2H, SCH_2), 7.4–7.51 (m, 5H, Ph), 10.9 (s, 1H, N*H*); δ_C (200 MHz, $CDCl_3$) 13.4, 21.8, 31.0, 31.03, 126.8, 129.1, 129.5, 132.2, 144.8, 155.6; *m/z* 249 (M^+, 32), 193 (100), 136 (10).

The other 4-substituted-3-butylthio-Δ^2-1,2,4-triazolin-5-ones prepared by adopting the above procedure are listed below.

2.4.2. 4-Methyl-3-butylthio-Δ^2-1, 2,4-triazolin-5-one (5b). White needles, mp 84°C; (Found: C, 44.87; H, 6.91; N, 22.39; S, 17.21. $C_7H_{13}N_3OS$ requires C, 44.92; H, 6.95; N, 22.46; S, 17.11%); R_f (45% petroleum ether/ethyl acetate) 0.53; ν_{max} (KBr, pellet) IR (KBr, pellet): 3250, 2900, 1700, 1510 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.9 (t, *J*=7.3 Hz, 3H, *Me*), 1.43 (m, 2H, CH_2CH_2Me), 1.7 (m, 2H, CH_2CH_2Me), 2.89 (t, *J*=7.1 Hz, 2H, SCH_2), 3.19 (s, 3H, N*Me*), 9.21 (s, 1H, N*H*); δ_C (200 MHz, $CDCl_3$) 13.5, 21.7, 27.4, 31.3, 31.5, 144.8, 156.3. MS: 187 (M^+, 16), 131 (100), 74 (16).

2.4.3. 4-Ethyl-3-butylthio-Δ^2-1,2,4-triazolin-5-one (5c). White needles, mp 70°C; (Found: C, 47.62; H, 7.32; N, 20.75; S, 16.01. $C_8H_{15}N_3OS$ requires C, 47.76; H, 7.46; N, 20.89; S, 15.92%); R_f (25% petroleum ether/ethyl acetate) 0.50; ν_{max} (KBr, pellet) 3230, 2900, 1700, 1690, 1510 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.9 (t, *J*=7.1 Hz, 3H, *Me*), 1.29 (t, *J*=7.3 Hz, 3H, *Me*), 1.43 (m, 2H, CH_2CH_2Me), 1.7 (m, 2H, CH_2CH_2Me), 3.07 (t, *J*=6.8 Hz, 2H, SCH_2), 3.69 (q, *J*=7.3 Hz, 2H, NCH_2), 9.21 (s, 1H, N*H*); δ_C (200 MHz, $CDCl_3$) 13.5, 14.2, 21.8, 31.3, 31.5, 36.6, 144.5, 155.8; *m/z* 202 (M+1, 17), 145 (100), 117 (35), 74 (23).

2.4.4. X-Ray structural analysis of compound (5c). *Crystal data.* $C_8H_{15}N_3OS$, *M*=201.29, monoclinic, $P2_1/ca$=11.233 (11), *b*=7.992 (4), *c*=12.225 (5) Å, α=90.00, β=93.48 (6), γ=90.00°, *B*=1095.5 (13) Å^3, *Z*=4, D_c=1.220 mg/m^3, μ (Mo-Kα)=0.265 mm^{-1}, F (000)= 432, 2237 (2135) independent reflections were measured on an Enraf–Nonius CAD4 Diffractometer with Mo-Kα radiation using ω scans. The final *wR* (F_2) was 0.3999 and *R*1=0.2458 (all data). The structure was solved using direct method and refined by full-matrix least squares on F^2. Further details of the crystal structure investigation have been deposited at the Cambridge Crystallographic Data Center. CCDC 149010. XTAL 3.4[13] version was employed for the data reduction. The solution and refinement for the crystal data was obtained using SHELXS-96[14] and SHELXL-96[15] program, respectively.

2.5. General procedure for the synthesis of 5(d–f)

A suspension of 1-*p*-chlorophenyl-2-thiobiurea **3e** (2.45 g, 0.01 mol) in ethanol (10 ml) containing concentrated

hydrochloric acid (0.5 ml) was refluxed with benzyl chloride (1.2 ml, 0.01 mol) at 100°C for 4 h. The solvent was then removed and the white product obtained was purified by dissolution in dilute alkali. The alkaline solution on neutralization afforded **5d**. It was crystallized from EtOH/H_2O mixture (1:1).

2.5.1. 4-*p*-Chlorophenyl-3-benzylthio-Δ^2-1,2,4-triazolin-5-one (5d). White needles, mp 202°C; (Found: C, 56.99; H, 3.64; N, 13.33; S, 10.29. $C_{15}H_{12}N_3OSCl$ requires C, 56.69; H, 3.78; N, 13.23; S, 10.08%); R_f (45% petroleum ether/ethyl acetate) 0.51; ν_{max} (KBr, pellet) 3400, 3050, 2850, 1700, 1510, 840, 720 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.18 (s, 2H, SC*H*$_2$), 7.23–7.44 (m, 9H, Ph), 11.97 (s, 1H, N*H*); δ_C (300 MHz, DMSO-d_6) 35.1, 126.7, 127.1, 127.6, 127.9, 128.4, 130.0, 133.2, 134.9, 141.5, 153.5; *m/z* 318 (M^+, 29), 169 (5), 125 (11), 91 (100).

The other 4-substituted-3-benzylthio-Δ^2-1,2,4-triazolin-5-ones prepared by adopting the above procedure are listed below.

2.5.2. 4-Propyl-3-benzylthio-Δ^2-1,2,4-triazolin-5-one (5e). White needles, mp 92°C; (Found: C, 57.76; H, 6.17; N, 16.82; S, 12.88. $C_{12}H_{15}N_3OS$ requires C, 57.83; H, 6.02; N, 16.87; S, 12.85%); R_f (25% petroleum ether/ethyl acetate) 0.48; ν_{max} (KBr, pellet) 3400, 3050, 2900, 1700, 1510, 710 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (t, *J*=7.3 Hz, 3H, *Me*), 1.64 (m, 2H, C*H*$_2$Me), 3.46 (t, *J*=7.0 Hz, 2H, NC*H*$_2$), 4.26 (s, 2H, SC*H*$_2$), 7.28–7.35 (m, 5H, Ph), 10.28 (s, 1H, N*H*); δ_C (300 MHz, DMSO-d_6) 10.9, 22.1, 36.7, 43.1, 127.9, 128.7, 129.0, 136.0, 144.1, 155.9; *m/z*: 249 (M^+, 17), 149 (5), 91 (100).

2.5.3. 4-Butyl-3-benzylthio-Δ^2-1,2,4-triazolin-5-one (5f). White needles, mp 72°C; (Found: C, 59.13; H, 6.28; N, 15.91; S, 12.22. $C_{13}H_{17}N_3OS$ requires C, 59.32; H, 6.46; N, 15.96; S, 12.17%); R_f (25% petroleum ether/ethyl acetate) 0.44; ν_{max} (KBr, pellet) 3350, 3100, 2950, 1690, 1520, 720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.9 (t, *J*=7.2 Hz, 3H, *Me*), 1.31 (m, 2H, CH_2CH_2Me), 1.55 (m, 2H,C*H*$_2$CH$_2$Me), 3.49 (t, *J*=7.0 Hz, 2H, NC*H*$_2$), 4.26 (s, 2H, SC*H*$_2$), 7.29–7.35 (m, 5H, Ph), 10.38 (s, 1H, N*H*); δ_C (300 MHz, $CDCl_3$) 13.5, 19.7, 30.8, 36.7, 41.4, 127.9, 128.7, 128.9, 136.1, 143.9, 156; *m/z* 263 (M^+, 50), 207 (24), 91 (100).

2.6. General procedure for the synthesis of 5(g–i)

A mixture of 1-*p*-tolyl-2-thiobiurea **3b** (2.24 g, 0.01 mol), MeI (7 ml, 0.01 mol) and hydroiodic acid (2 M, 2 ml) in dry ethanol (10 ml) was refluxed at 40°C for 8 h. The solvent was removed by distillation under reduced pressure. The white solid obtained was dissolved in NaOH (2 M, 10 ml). The crude mixture (TLC) was chromatographed on a column of silica gel with petroleum ether/ethyl acetate (25:75) to give **5g**.

2.6.1. 4-*p*-Tolyl-3-methylthio-Δ^2-1,2,4-triazolin-5-one (5g). White needles, mp 196°C; (Found: C, 54.34; H, 4.87; N, 19.21; S, 14.52. $C_{10}H_{11}N_3OS$ requires C, 54.29; H, 4.98; N, 19.0; S, 14.48%); R_f (25% petroleum ether/ethyl acetate) 0.44; ν_{max} (KBr, pellet) 3450, 3050, 2900, 1690, 1510, 820 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.41 (s, 3H, S*Me*), 2.49 (s, 3H, C_6H_4*Me*), 7.26 (d, *J*=8.7 Hz, 2H, Ph), 7.28 (d, *J*=8.7 Hz, 2H, Ph), 10.71 (s, 1H, N*H*); δ_C (300 MHz, DMSO-d_6) 13.1, 21.3, 126.5, 129.5, 130.2, 139.2, 145.6, 155.7; *m/z* 221 (M^+, 96), 206 (10), 149 (16), 88 (100).

The other 4-substituted-3-methylthio-Δ^2-1,2,4-triazolin-5-ones prepared by adopting the above procedure are listed below.

2.6.2. 4-*p*-Anisyl-3-methylthio-Δ^2-1,2,4-triazolin-3-one (5h). White needles, mp 220°C; (Found: C, 50.71; H, 4.45; N, 17.68; S, 13.61. $C_{10}H_{11}N_3O_2S$ requires C, 50.63; H, 4.64; N, 17.72; S, 13.5%); R_f (30% petroleum ether/ethyl acetate) 0.51; ν_{max} (KBr, pellet) 3450, 3150, 2900, 1720, 1510, 820 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.49 (s, 3H, S*Me*), 3.85 (s, 3H, O*Me*), 7.03 (d, *J*=9.0 Hz, 2H, Ph), 7.31 (d, *J*=9.0 Hz, 2H, Ph), 9.95 (s, 1H, N*H*); δ_C (300 MHz, DMSO-d_6) 14.2, 55.5, 114.8, 124.8, 128.2, 147.2, 155.9, 160.0; *m/z* 237 (M^+, 100), 222 (34), 193 (5), 88 (22).

2.6.3. 4-Ethyl-3-methylthio-Δ^2-1,2,4-triazolin-3-one (5i). White needles, mp 95°C; (Found: C, 37.82; H, 5.48; N, 26.23; S, 20.33. $C_5H_9N_3OS$ requires C, 37.74; H, 5.66; N, 26.42; S, 20.13%); R_f (20% petroleum ether/ethyl acetate) 0.48; ν_{max} (KBr, pellet) 3450, 2950, 1710, 1520 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.1 (t, *J*=7.0 Hz, 3H, *Me*), 2.48 (s, 3H, S*Me*), 3.69 (q, *J*=7.0 Hz, 2H, NC*H*$_2$), 10.22 (s, 1H, N*H*); δ_C (300 MHz, DMSO-d_6) 14.07, 14.1, 36.56, 144.1, 155.9; *m/z* 159 (M^+, 100), 144 (30), 116 (8), 43 (35).

2.7. General procedure for the synthesis of 5(j–l)

To a mixture of 1-*p*-tolyl-2-thiobiurea **3b** (2.24 g, 0.01 mol) in dry ethanol and hydrochloric acid (2N, 2 ml), allylchloride (1 ml) was added and refluxed at 50°C for 11 h. The crude mixture obtained after the removal of the solvent was cooled at 0°C and the white solid obtained was triturated with NaOH (2 M, 15 ml). Neutralization of the the alkaline filtrate by the addition of hydrochloric acid (2N, 15 ml) afforded **5j**. It was collected and crystallized from a mixture of ethanol/water (1:1).

2.7.1. 4-*p*-Tolyl-3-allylthio-Δ^2-1,2,4-triazolin-5-one (5j). White needles, mp 119°C; (Found: C, 58.04; H, 5.13; N, 16.92; S, 12.93. $C_{12}H_{13}N_3OS$ requires C, 58.29; H, 5.26; N, 17.0; S, 12.95%); R_f (40% petroleum ether/ethyl acetate) 0.48; ν_{max} (KBr, pellet) 3400, 3050, 3010, 1700, 1510, 840 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.49 (s, 3H, C_6H_4Me), 3.5 (d, *J*=6.6 Hz, 2H, SC*H*$_2$), 5.2 (m, 2H, CH=C*H*$_2$), 5.79 (m, 1H, C*H*=CH$_2$), 7.08 (d, *J*=8.8 Hz, 2H, Ph), 7.31 (d, *J*=8.8 Hz, 2H, Ph), 10.9 (s, 1H, N*H*); δ_C (200 MHz, $CDCl_3$) 21.2, 34.1, 119.2, 126.6, 129.4, 130.2, 132.1, 139.4, 144.1, 155.6.; *m/z* 247 (M^+, 38), 204 (100), 149 (32).

The other 4-substituted-3-allylthio-Δ^2-1,2,4-triazolin-5-ones prepared by adopting the above procedure are listed below.

2.7.2. 4-*p*-Anisyl-3-allylthio-Δ^2-1,2,4-triazolin-5-one (5k). White needles, mp 123°C; (Found: C, 54.84; H, 5.15; N, 15.8; S, 12.38. $C_{12}H_{13}N_3O_2S$ requires C,54.75; H, 4.94; N, 15.97; S, 12.17%); R_f (40% petroleum ether/ethyl acetate)

0.43; ν_{max} (KBr, pellet) 3400, 3150, 3050, 1690, 1510, 840 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.5 (d, J=6.5 Hz, 2H, SCH_2), 3.82 (s, 3H, O*Me*), 5.2 (m, 2H, CH=CH_2), 5.8 (m, 1H, CH=CH_2), 7.1 (d, J=9.0 Hz, 2H, Ph), 7.3 (d, J=9.0 Hz, 2H, Ph), 10.9 (s, 1H, N*H*); δ_C (200 MHz, $CDCl_3$) 34.1, 55.6, 114.8, 119.2, 124.7, 128.3, 132.2, 144.3, 155.8, 160.1; *m*/*z* 263 (M^+, 35), 220 (100), 165 (45).

2.7.3. 4-*p*-Phenetyl-3-allylthio-Δ^2-1,2,4-triazolin-5-one (5l). White needles, mp 139°C; (Found: C, 56.38; H, 5.30; N, 15.23; S, 11.61. $C_{13}H_{15}N_3O_2S$ requires C, 56.32; H, 5.42; N, 15.16; S, 11.55%); R_f (35% petroleum ether/ethyl acetate) 0.45; ν_{max} (KBr, pellet) 3350, 3050, 3040, 1700, 1510, 840 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.41 (t, J=7.0 Hz, 3H, *Me*), 3.61 (d, J=6.6 Hz, 2H, SCH_2), 4.1 (q, J=7.0 Hz, 2H, OCH_2), 5.19 (m, 2H, CH=CH_2), 5.8 (m, 1H, CH=CH_2), 7.0 (d, J=8.9 Hz, 2H, Ph), 7.3 (d, J=8.9 Hz, 2H, Ph), 10.2 (s, 1H, N*H*); δ_C (200 MHz, $CDCl_3$) 14.7, 33.9, 63.8, 115.2, 119.2, 124.3, 128.2, 132.1, 144.3, 155.7, 159.4; *m*/*z* 277 (M^+, 24), 234 (37), 179 (16).

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