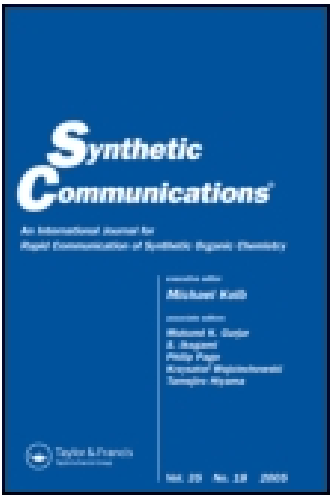

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SYNTHESIS OF SUBSTITUTED-Δ^2-1,2,4-TRIAZOLIN-5-ONES AND S-SUBSTITUTED ISOTHIOBIUREAS FROM 1-ARYL/ALKYL-6-PHENYL-2-THIOBIUREAS

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SYNTHESIS OF SUBSTITUTED-Δ^2-1,2,4-TRIAZOLIN-5-ONES AND *S*-SUBSTITUTED ISOTHIOBIUREAS FROM 1-ARYL/ALKYL-6-PHENYL-2-THIOBIUREAS

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ABSTRACT

Reaction of 1-aryl/alkyl-6-phenyl-2-thiobiureas **1** with BnCl and BuI in neutral medium at reflux temperature resulted in the formation of the S-alkylated isothiobiureas **2** and 1,2,4-triazolin-5-one derivatives **3**. A convenient route to **2** is also reported.

Compounds containing twinned double bonds, such as carbodiimides and iso (thio) cyanate esters, undergo rapid addition reactions with hydrazino[1–3] and amidino groups.[2,4] Reaction of 4-alkylthiosemicarbazides with arylcyanamides afforded 4-alkyl-3-arylamino-1,2,4-triazoline-5-thiones.[5] However, 1-phenylacetyl-4-substituted thiosemicarbazides undergo reaction in alkaline and acidic media to yield 3-benzyl-Δ^2-1,2,4-triazoline-5-thiones and 2-amino-5-benzyl-1,3,4-thiadiazoles, respectively.[6] Quite interestingly, it has been reported that 1-acyl-6-aryl/alkyl-2,5-dithiobiureas, on reaction with *p*-toluenesulphonyl chloride in the presence of triethylamine,[7,8] or

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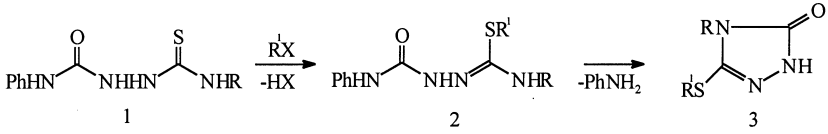
a brominating agent,[7] or with methyl iodide in the absence of a base,[7] yielded 1,3,4-thiadiazole derivatives. On the other hand, 1-acyl-6-aryl/alkyl-2,5-dithiobiurea derivative reacts with sodium ethanolate to afford a 1,2,4-triazoline-5-thione derivative only.[9] Cyclization reactions of 1,6-disubstituted-2-thiobiureas with alkyl halides have not been reported to date. Hence, our studies were mainly in that direction to understand the reaction mechanism and its pathway.

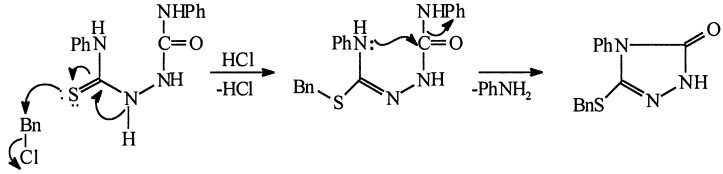
The reaction of **1a** with BnCl in ethanol at reflux temperature was found to afford 1,6-diphenyl-2-S-benzyl isothiobiurea **2a** and 4-phenyl-3-benzylthio-Δ^2-1,2,4-triazolin-5-one **3a.** Because of the high polarisability of the SH bond, and also of the electropositive character of the sulfur atom when compared to nitrogen, it is the SH group that undergoes preferential benzylation over the NH. The acid produced during the course of S-benzylation favors the cyclization of **2a** to yield **3a** (Scheme 1).



R: a = C_6H_5, b = *p*-$CH_3C_6H_4$, c = *p*-$CH_3OC_6H_4$, d = *p*-ClC_6H_4 , e = Me, f = Et, g = Pr

Scheme 1.

During cyclization, the more basic nitrogen atom at position 1 makes a nucleophilic attack on the carbonyl carbon, thereby expelling aniline, resulting in the formation of **3a**. The presence of aniline in the reaction mixture was detected by dye test (Scheme 2, mechanism).



Scheme 2.

The above reaction, carried out in neutral medium, afforded a 60% yield of **2a** and 30% yield of **3a**, whereas a mere repetition of the same reaction in hydrochloric acid afforded a complete conversion. This indicates that the acid generated in situ or added is a must for the cyclization reaction.

The acid added protonates the N-6, thereby enhancing the elimination of amine. The isolation of **2a** and its acid-catalyzed cyclization to **3a** confirms the reaction pathway. Further proof for the structure **2a** is arrived at from its alternative synthesis by the reaction of 4-phenyl-3-S-benzylisothiosemicarbazide with phenyl isocyanate in dry acetonitrile. Compounds **1 (a–f)** undergo similar reaction with BuI (Tables 1, 2)

On similar lines, we found that reaction of 1-aryl/alkyl-2-thiobiureas with alkyl halides in acidic and neutral media resulted in the exclusive formation of 1,2,4-triazolin-5-one derivatives, which are identical to the products formed in the case of 1,6-disubstituted-2-thiobiureas. The above reaction once again highlights the mode of cyclization that occurs by the attack of N-1 on C-5, resulting in the formation of five-membered heterocycles. In conclusion, we have developed a simple and convenient method for the synthesis of five-membered heterocycles from extended urea-like chain compounds.

Table 1. 1-Aryl/alkyl-6-phenyl-2-S-substituted Isothiobiureas **2**

Compounds	R	Substituent	M.p. (°C)
a	C_6H_5	Bn	237–238
b	*p*-$CH_3C_6H_4$	Bn	165
c	Et	Bn	143
d	Pr	Bn	147
e	*p*-$H_3COC_6H_4$	Bu	231–232
f	*p*-ClC_6H_4	Bu	217
g	Me	Bu	117–118
h	Et	Bu	117

Table 2. 4-Aryl/alkyl-3-substituted Thio-Δ^2-1,2,4-triazolin-5-ones **3**

Compounds	R	Substituent	M.p. (°C)
a	C_6H_5	Bn	157
b	*p*-$CH_3C_6H_4$	Bn	186–187
c	Et	Bn	93–94
d	Pr	Bn	91–92
e	*p*-$H_3COC_6H_4$	Bu	122
f	*p*-ClC_6H_4	Bu	109–110
g	Me	Bu	84
h	Et	Bu	70

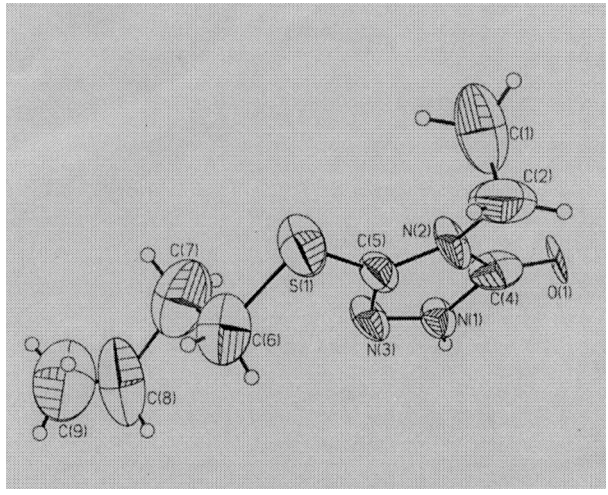


Figure 1. The ortex diagram of 4-ethyl-3-butylthio-Δ^2-1,2,4-triazolin-5-one.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were taken on a Perkin Elmer RX1 spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 on a BRUCKER-300 spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded at 70 eV ionizing voltage on a Jeol-D300 MS instrument. The elemental analyses were performed by the National Chemical Laboratory, Pune. The crystal structure of **3h** was determined on an Enraf-Nonius CAD4 diffractometer with Mo-Kα radiation. All the isothio cyanates were prepared according to literature procedure.[10]

Preparation of 1-Aryl/alkyl-6-phenyl-2-thiobiureas 1 (a–f)

Phenyl isocyanate (1.19 mL, 0.01 mol) was added dropwise to a suspension of 4-aryl/alkylthio semicarbazide (0.01 mol) in acetonitrile (15 mL) with efficient stirring. The white product that separated after 10 min was collected and triturated with 2N alkali. Neutralization of the alkaline filtrate yielded **1 (a–f)**. It was crystallized from DMF: ethanol (1:1) as white needles. All the required 4-aryl/alkylthiosemicarbazides were obtained by the reaction of corresponding isothiocyanates with hydrazine hydrate at 0°C in ethanolic medium.

Preparation of 4-Aryl/alkyl-3-benzyl/butylthio-Δ^2-1,2,4-triazolin-5-ones 3 (a–h)

A suspension of **1** (**a–f**) (0.01 mol) in ethanol containing 2 mL concentrated HCl/HI was refluxed with BnCl/BuI (0.01 mol). The solid obtained after 4 h was dissolved in alkali. Neutralization of the alkaline filtrate yielded **3** (**a–h**). Purification was done either by column chromatography on silica or by crystallization from aqueous ethanol (1:1). The triazoles obtained are listed below. The reaction was repeated in neutral medium for 4 h and the residue obtained on TLC examination indicated the presence of two compounds. It was triturated with 2N alkali and acidified to obtain compounds **3** (**a–h**). The alkali-insoluble products were identified as the open-chain S-alkylated isothiobiureas **2** (**a–h**).

3a: IR (KBr)ν: 3450, 3050, 2900, 1690, 1590, 1510, 760 cm^{-1}. ^1H NMR δ: 4.21 (s, 2H, SCH_2), 7.29–7.51 (m, 10H, Ar), 9.95 (s, 1H, NH). ^{13}C NMR δ: 35.91, 124.29, 126.78, 127.84, 128.68, 129.10, 129.49, 132.15, 135.89, 144.24, 155.64. MS, m/z: 283 (M^+, 20), 240 (M-43, 25), 135 (6), 91 (100). Anal. calc. for $C_{15}H_{13}N_3OS$: C, 63.60; H, 4.59; N, 14.84; S, 11.31. Found: C, 63.46; H, 4.19; N, 15.01; S, 11.81.

3b: IR (KBr)ν: 3400, 3050, 2950, 1700, 1510, 815, 725 cm^{-1}. ^1H NMR δ: 2.4 (s, 3H), 4.18 (s, 2H, SCH_2), 7.28–7.50 (m, 9H, Ar), 10.1 (s, 1H, NH). MS, m/z: 297 (M^+, 20), 254 (7), 149 (31), 91(100).

3c: IR (KBr)ν: 3450, 3050, 2900, 1710, 1515, 720 cm^{-1}. ^1H NMR δ: 1.19 (t, 3H, J = 7.24 Hz), 3.58 (q, 2H, J = 7.24 Hz, NCH_2), 4.26 (s, 2H, SCH_2), 7.28–7.35 (m, 5H, Ar), 9.99 (s, 1H, NH).^{13}C NMR δ: 14.12, 36.57, 36.80, 127.94, 128.77, 128.99, 136.09, 143.79, 155.75.

3d: IR (KBr)ν: 3400, 3050, 2900, 1700, 1510, 710 cm^{-1}. ^1H NMR δ: 0.88 (t, 3H, J = 7.3 Hz),1.64 (m, 2H), 3.46 (t, 2H, J = 7.2, 7.5 Hz, NCH_2), 4.26 (s, 2H, SCH_2), 7.26–7.35 (m, 5H, Ar), 10.28 (s, 1H, NH). ^{13}C NMR δ: 10.95, 22.09, 36.66, 43.09, 127.88, 128.71, 128.96, 136.03, 144.12, 155.95. MS, m/z: 249 (M^+, 22), 149 (3), 91 (100). Anal. calc. for $C_{12}H_{15}N_3OS$: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.79; H, 6.16; N, 16.83.

3e: IR (KBr)ν: 3250, 3100, 2950, 1720, 1520, 1260, 840 cm^{-1}. ^1H NMR δ: 0.91 (t, 3H), 1.41 (m, 2H), 1.7 (m, 2H), 2.98 (t, 2H, SCH_2), 3.89 (s, 3H, OMe), 7.01 (d, 2H, Ar), 7.31 (d, 2H, Ar), 11.01 (s, 1H, NH). ^{13}C NMR δ: 13.46, 21.79, 30.86, 31.06, 55.56, 114.79, 124.79, 128.24, 145.26, 155.89, 160.05. MS, m/z: 279 (M^+, 52), 223 (100), 149 (32).

3f: IR (KBr)ν: 3250, 3100, 2900, 1690, 1520, 1220, 790 cm^{-1}. ^1H NMR δ: 0.9 (t, 3H), 1.42 (m, 2H), 1.7 (m, 2H), 3.10 (t, 2H, SCH_2), 7.37 (d, 2 H, Ar), 7.5 (d, 2H, Ar), 10 (s, 1H, NH).

3g: IR (KBr)ν: 3200, 2900, 2800, 1700, 1510, 760 cm^{-1}. ^1H NMR δ: 0.9 (t, 3H), 1.43 (m, 2H), 1.7 (m, 2H), 2.89 (t, 2H, SCH_2), 3.19 (s, 3H, NCH_3),

9.21 (s, 1H, NH). ^{13}C NMR δ: 13.48, 21.74, 27.42, 31.26, 31.49, 144.79, 156.28. MS, m/z: 187 (M^+, 16), 149 (5), 131 (100), 74 (16).

Preparation of 1,6-Disubstituted-2-S-benzyl/butyl-isothiobiureas 2 (a–h)

To an etherial solution (dry) of 4-phenyl-3-S-benzyl/butylisothiosemicarbazide (0.01 mol) prepared by the condensation of 4-aryl/alkylthiosemicarbazide with BnCl/BuI, phenyl isocyanate (0.01 mol) was added with efficient stirring. The solid obtained was collected and washed with 2N alkali, and finally crystallized from ethanol as white needles.

2a: IR (KBr)ν: 3450, 3400, 3390, 3150, 2950, 1670, 1510, 720 cm^{-1}. ^{1}H NMR δ: 4.24 (s, 2H, SCH_2), 6.63, 7.12, 7.14 (three NH protons), 7.26–7.42 (m, 15H, Ar) MS, m/z: (M^+, absent), 253 (M-123, 4), 149 (2), 121 ($C_6H_5CONH_2^+$, 8), 91 (100). Anal. calc. for $C_{21}H_{20}N_4OS$: C, 67.02; H, 5.32, N, 14.89. Found: C, 68.01; H, 5.52; N, 13.79.

2b: IR (KBr)ν: 3500, 3450, 3390, 3050, 2900, 1690, 1520, 820 cm^{-1}. ^{1}H NMR δ: 2.5 (s, 3H), 4.38 (s, 2H, SCH_2), 7.97, 8.18, 9.77 (three NH protons), 7.18–7.42 (m, 14H, Ar). MS. m/z (M^+, absent), 267 (5), 149 (10), 106 (8), 91(100).

2c: IR (KBr)ν: 3450, 3400, 3350, 3150, 2950, 1690, 1515, 715 cm^{-1}. ^{1}H NMR δ: 1.2 (t, 3H), 3.61 (q, 2H), 4.2 (s, 2H, SCH_2), 7.87, 8.3, 9.21 (three NH protons), 7.25–7.48 (m, 10H, Ar). MS. m/z: (M^+, absent), 194 (5), 150 (13), 93 (100), 91 (80).

2d: IR (KBr)ν: 3450, 3430, 3400, 3250, 3000, 1700, 1510, 720 cm^{-1}. ^{1}H NMR δ: 0.89 (t, 3H), 1.65 (m, 2H), 3.5 (t, 2H, NCH_2), 4.30 (s, 2H, SCH_2), 8.4, 8.48, 9.21 (three NH protons), 7.26–7.43 (m, 10H, Ar). MS, m/z: (M^+, absent), 218 (100), 91 (22). Anal. calc. for $C_{18}H_{22}N_4OS$: C, 63.16; H, 6.43; N, 16.37. Found: C, 62.98; H, 6.13; N, 16.21.

2e: IR (KBr)ν: 3400, 3200, 3150, 3050, 2910, 1590, 1510, 810 cm^{-1}. ^{1}H NMR δ: 0.99 (t, 3H), 1.41 (m, 2H), 1.59 (m, 2H), 2.79 (t, 2H, SCH_2), 3.82 (s, 3H, OMe), 6.55, 6.98, 8.27 (three NH protons), 7.13–7.24 (m, 5H, Ar), 7.26 (d, 2H, Ar), 7.34 (d, 2H, Ar). MS. m/z: (M^+, absent), 212 (83), 135 (3), 121 (4), 93 (100).

2f: IR (KBr)ν: 3450, 3200, 3150, 3050, 2900, 1590, 1490, 820 cm^{-1}. ^{1}H NMR δ: 0.92 (t, 3H), 1.44 (m, 2H), 1.72 (m, 2H), 2.93 (t, 2H, SCH_2), 6.95, 6.97, 8.29 (three NH protons), 7.25–7.31 (m, 5H, Ar), 7.45 (d, 2H, Ar), 7.48 (d, 2H, Ar). ^{13}C NMR δ:13.57, 21.66, 30.06, 31.07, 119.19, 119.93, 122.21, 122.94, 128.39, 128.77, 128.89, 138.41, 139.52, 153.25. Anal. calc. for $C_{18}H_{21}N_4OSCl$: C, 57.37; H, 5.58; N, 14.87. Found: C, 57.42; H, 5.54; N, 14.92.

2g: IR (KBr)ν: 3410, 3300, 3150, 2850, 1590, 1220 cm^{-1}. ^1H NMR δ: 0.94 (t, 3H), 1.44 (m, 2H), 1.71 (m, 2H), 2.96 (t, 2H, SCH_2), 3.01 (s, 3H, NCH_3), 6.05, 8.09, 9.53 (three NH protons), 7.29–7.71 (m, 5H, Ar). ^{13}C NMR δ: 13.61, 21.61, 30.44, 31.14, 32.14, 119.29, 122.94, 128.75, 138.3, 153.71, 155.44. MS, m/z: 280 (M^+, 9), 224 (8), 212 (10), 135 (46), 91 (100). Anal. calc. for $C_{13}H_{20}N_4OS$: C, 55.71; H, 7.4; N, 20.0. Found: C, 55.85; H, 7.18; N, 19.06.

2h: IR (KBr)ν: 3450, 3400, 3350, 2850, 1600, 1310 cm^{-1}. ^1H NMR δ: 0.93 (t, 3H), 1.29 (t, 3H), 1.43 (m, 2H), 1.7 (m, 2H), 3.07 (t, 2H, SCH_2), 3.69 (q, 2H, NCH_2), 6.08, 8.1, 9.41 (three NH protons), 7.29–7.72 (m, 5H, Ar). MS. m/z: 294 (M^+, 7), 239 (13), 136 (42), 93 (100).

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