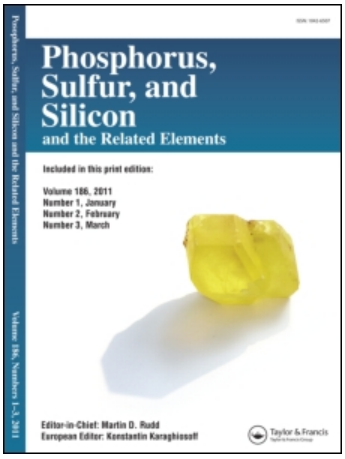

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A Convenient Synthesis of New [1,2,4]Triazolo[3′,4′:2,3][1,3]thiazolo [4,5-b]quinoxalines

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New derivatives of 3-substitued [1,2,4]triazolo[3′,4′;2,3][1,3]triazolo[4,5-b]quinoxalines ***6*** *have been prepared by the cyclocondensation of [1,3]thiazolo[4,5-b]quinoxaline-2(3H) one hydrazone* ***5*** *with aroyl chlorides, trimethylorthoformate, or triethylorthoacetate.*

Keywords 2,3-Dichloroquinoxaline; thiazoloquinoxaline; triazolothiazoloquinoxaline

Starting from biological considerations and due to our interest in the synthesis of polycyclic N-heterocycles,[1,2] it was decided to synthesize [1,2,4]triazolo [3′,4′:3][1,3]thiazolo[4,5-b] quinoxaline derivatives **6**(**a–e**). A literature search provided only one example describing this ring system.[3]

We reacted N′-butyl-2(1-methylethylidene)-1-hydrazine carbothiomide **1** with 2,3-dichloroquinoxaline **2**, similar to what had already been reported in the literature[4,5] (Scheme 1). Structure **3** was proposed for the product characterized by its spectral data. When this compound was subjected to diazotization at room temperature, the 3-amino moiety was removed to produce **4**. Subsequent treatment of this compound with hydrazine hydrochloride produced the desired intermediate **5**. The structures assigned to compounds **4** and **5** were substantiated by their spectral data (Table I). For example, the ^{1}H−NMR spectrum of compound **4** was devoid of the signal at δ 4.7 ppm for NH_2 group of the precursor **3**, but showed further downfield a peak at 9.3 ppm for the N-H ring proton, while **5** showed a signal at δ 10.5 ppm for the N-H

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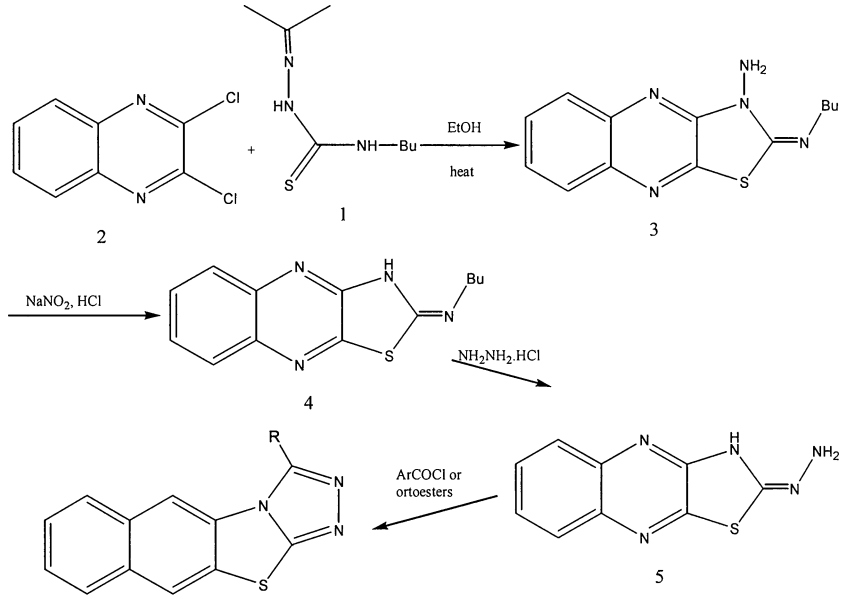
TABLE I Physical and Spectral Data of Thiaolo[4,5-b]quinoxalines

Entry	Reaction time (h)	Yield (%)	M.P. (°C)	Spectral data
1	2	62	59–61	^{1}H NMR: ($CDCl_3$), 8.4 (s, 1H, NH), 7.51 (s, 1H, NH), 3.5 (t, 2H, N-CH_2); 1.5 (m, 4H, —$(CH_2)_2$ (d, 6H, $2CH_3$), 1 (t, 3H, CH_3) IR (KBr disk). *υ*, 3250, 3200, 1640, 1200, m/z, 187 (M)
3	4	60	70	^{1}H NMR: ($CDCl_3$), 7.5–8 (m, 4H, NH, aromatic), 4.7 (s, 2H, NH_2), 3.4 (t, 2H, NCH_2), 1.6 (m, 4H, CH_2), IR (KBr disk): *υ* 1600, 475, 3350, m/z, 273
4	3	42	80	^{1}H NMR: ($CDCl_3$), 7.55–8 (m, 4H, aromatic) 3.75 (t, 2H, I-Ch_2); IR (KBr disk); *υ*, 3300–3500, 100, 1650, m/z, 258 (M)
5	5	47	230–235	^{1}H NMR: (DMSO-d6), 10.5 (s, 1H, NH, 7.8 (m, 4H, C_6H_4), 5.5 (s, 2H, NH_2; IR (KBr disk); *υ* 3300–3500, 3050, 1650, m/z, 217 (M)



6a:R = Ph, 6b:R = 2-Cl-C6H4, 6c: R = 4-Cl-C6H4
6d:R = Me, 6e:R = H

SCHEME 1

ring proton and a broad signal at 5.5 ppm for the NH_2 group, for which both were removed on deuteration.

The interaction of the intermediate **5** with aroyl chlorides, trimethylorthoformate, or triethylorthoacetate led to the tetracyclic compounds **6**, [1,2,4]triazolo[3′4′:2,3]thiazolo[4,5-b]quinoxalines. Assignment of structure **6** is supported by their analytical and spectral data (Table II, Scheme 1).

In conclusion, we have developed a convenient method for the conversion of N′-butyl-2(1-methylethyliden)-1-hydraziecarbothioamide into 3-substituded [1,2,4]triazolo[3′,4′;2,3][1,3]thiazolo[4,5-b]quinoxalines through cyclocondensation with aroyl chlorides and orthoesters.

EXPERIMENTAL SECTION

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR Spectra were obtained on a 4300 Shimadzu Spectrometers as KBr disks. The ^{1}H-NMR (100 MHz) spectra were recorded on a Bruker AC 100 Spectrometer in d_6 DMSO and $CDCl_3$ solution. Mass spectra were obtained from a Varian CH-7 instrument at 70 ev. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer.

N′-Butyl-2-(1-methyl ethyliden)-1-hydrazine-carbothioamid (1)

A mixture of n-butyl thiosemicarbazide (5.2 g, 35 mmol), and acetone (5.1 mL, 70 mmol) in absolute ethanol (20 mL) was heated under reflux for 2 h. The reaction mixture was then cooled to room temperature 2–3 drops of water were added, and it was allowed to stand at room temperature and gave a while crystalline solid (4 g, 62%, yield) m.p 59–61°C.

N-(3-Amino [1-3]thiazolo[4,5-b]quinoxaline-2-yliden)-2-yliden)-N-butylamine (3)

To a solution of compound **1** (1.78 g, 10 mmol) in absolute ethanol (50 mL), 2,3-dichloroquinoxaline (2 g, 10 mmol) was added. The solution was heated under reflux for 4 h then water (5 mL) was added and heating was continued for a further hour. The mixture then was allowed to cool to room temperature. To the reaction mixture, sodium hydroxide (5 g) in 10 mL, of H_2O was added and it was stirred for 8 h. The precipitate was filtered and washed with warm water to give an orange powder (1.23 g, 47% yield, m.p. 100–103).

TABLE II Analytical, Physical, and Spectral Data of [1,2,4]Trazolo[3′,4′:2,3][1,3]thiazolo[4,5-b]quinoxalines

Entry	Reaction time (h)	Yield (%)	M.P (°C)	Spectral data	Molecular formula	C% [cal.]	H% [cal.]	N% [cal.]	S% [cal.]
6a	5	26	70–75	H.NMR: ($CDCl_3$), 8.3 (m, 4H,C_6H_4),7.6 (m, 5H,C_6H_5), IR: 1680, 3050, 3100, 1250, m/z 303	$C_{16}H_9N_5S$	63.4 [63.35]	3.02 [2.99]	23.14 [23.09]	10.4 [10.57]
6b	5	29	176–178	H.NMR: ($CDCl_3$), 8 (m, 4H, C_6H_4, 7.5 (m, 4H,C_6H_4), IR: 750, 1650, 3050–3100, m/z: 338 (M)	$C_{16}H_8CIN_5S$	56.92 [56.89]	2.44 [2.39]	20.83 [20.73]	9.32 [9.49]
6c	6	40	157–160	H.NMR: ($CDCl_3$), 8.2 (m, 4H, ph), 7.5 (m, 4H, ph), IR: 800–850, 3050, 1100 m/z, 338 (M)	$C_{16}H_8CIN_5S$	56.95 [56.89]	2.42 [2.39]	20.8 [20.73]	9.3 [9.49]
6d	8	49	213–217	H.NMR: ($CDCl_3$), 7.8–8.2 (M 4H, ph), 2.6 (s, 3H, CH_3) IR, 1640, 1100, 1250m/z 141 (M)	$C_{11}H_7N_5S$	54.8 [54.76]	2.95 [2.92]	29.12 [29.03]	13.1 [13.29]
6e	4	50	205–210	H.NMR: ($CDCl_3$), 8.5 (s) 1H, CH), 7.9–8.4 (m, 4H, pH), 1R: 3100, 1640, m/z, 227(M)	$C_{10}H_5N_5S$	52.9 [52.85]	2.24 [2.22]	30.8 [30.82]	13.9 [14.11]

N-(Butyl-N-[1,3]thiazolo[4,5-b]quinoxaline-2(3H)-ylidenamine (4)

To a solution of the foregoing, compound **3** (2.73 g, 10 mmol) in conc. HCl (37.5 mL) a solution of sodium nitrite (2.5 M, 50 mL) was added dropwise at 0–5°C for 2–3 h. The reaction mixture was stirred at room temperature for a further 2 h. The solution was poured onto crushed ice; the precipitate was filtered off and washed with warm water to give the title compound (2.0 g, 77% yield, m.p. 86–90°C.)

[1,3]Thiazolo[4,5-b]quinoxalin-2(3H)-one Hydrazone (5)

A solution of hydrazine monohydrochloride (0.5 g), compound **4** (0.5 g, 2 mmol), and hydrazine monohydrate (1 mL) in methanol (15 mL) was heated under reflux for 5 h. The solution was reduced in volume under reduced pressure, then water was added (30 mL) and the precipitate was collected after 0.5 h as a green powder (0.2 g, 47% yield, m.p. 230–235°C).

Unsubstituted or 3-Substituted [1,2,4]triazolo[3′4′:2,3][1,3]-thiazolo[4,5-b]quinoxalione (6)

Method A

Compound **5** (0.217 g, 1 mmol) and aroyl chloride (6.0 mL) was heated under reflux for 5 h. After completion of the reaction, which was monitored by TLC, an oily mixture was obtained. Sodium hydroxide (0.5 M) was added with stirring at room temperature to pH 6–7 for 0.5 h. The mixture then was extracted with chloroform (2 × 10 mL); the solvent was evaporated to dryness to get the desired compound **6** (**a–c**) (data in Table 1).

Method B

Compound **5** (0.217 g, 1 mmol) was heated under reflux either with triethyl orthoacetate (6 mL) in acetic acid for 8 h or with trimethyl orthoformate (6 mL) for 4–5 h. The solvent was removed in vaccu to obtain the desired product as yellow powder (data in Table I).

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