Heterocyclization of 2,4-Disubstituted Thiosemicarbazides with Haloketones

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2,4-Disubstituted thiosemicarbazides were allowed to react with α-bromoacetophenone to give the anticipated 2,3-dihydro-6*H*-1,3,4-thiadiazines, whereas with β-propiophenone and γ-butyrophenone to afford the unexpected 2,3-dihydro-1,3,4-thiadiazole. The reaction mechanism was also discussed.

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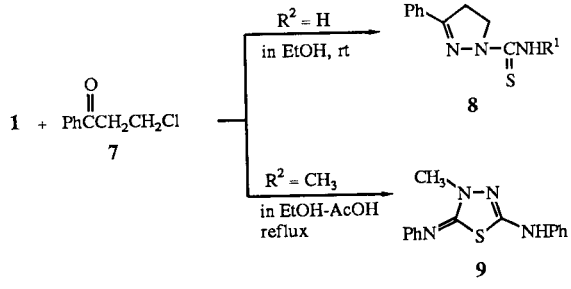
Thiosemicarbazides are versatile compounds which have been extensively used in the preparation of heterocyclic ring systems. Although the cyclization reactions of haloketones with 4-substituted thiosemicarbazides are recently known to result in the different heterocyclization by varying the chain length between the carbonyl group and the halogen atom [1-4], there has been little report of the reaction of 2,4-disubstituted thiosemicarbazides. We here report the cyclization reactions of 2,4-disubstituted thiosemicarbazides with α-, β- and γ-haloketones.

The reactions of 4-substituted thiosemicarbazides **1a** with α-bromoacetophenone **2** in warm 2*M* hydrochloric acid solution initially provide the corresponding thiosemicarbazones **3**, followed by ready cyclization to 2-amino-1,3,4-thiadiazines **4** in boiling ethanol [1]. 2,4-Disubstituted thiosemicarbazides **1b** also reacted with **2** in ethanol at room temperature in the absence of acid catalyst to give the thiosemicarbazones **5**, which undergo the ready cyclization by vigorous stirring in a mixture of 5% sodium hydroxide and dichloromethane at room temperature to 5-phenyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **6** (Scheme 1). The spectral data and the elemental analyses of the compounds **5** and **6** are summarized in Table I.

The analogous reaction of 4-methylthiosemicarbazide **1a** ($R^1 = CH_3$) with β-chloropropiophenone **7** in boiling propanol affords dihydro-1*H*-pyrazole **8** ($R^1 = CH_3$) [3]. The similar cyclization [4] is observed in the reaction of thioaroylhydrazine with **7**. We also attempted the same reaction under milder reaction condition by stirring in ethanol at room temperature and obtained the corresponding 4,5-dihydro-3-phenyl-1*H*-pyrazole-1-carbothioamides **8**, without being isolated a trace of thiosemicarbazone intermediates.

Scheme 2



On the other hand, in the reaction of 2-methyl-4-phenylthiosemicarbazide **1b** (R^1 = Ph) with **2**, we found that this

Scheme 1

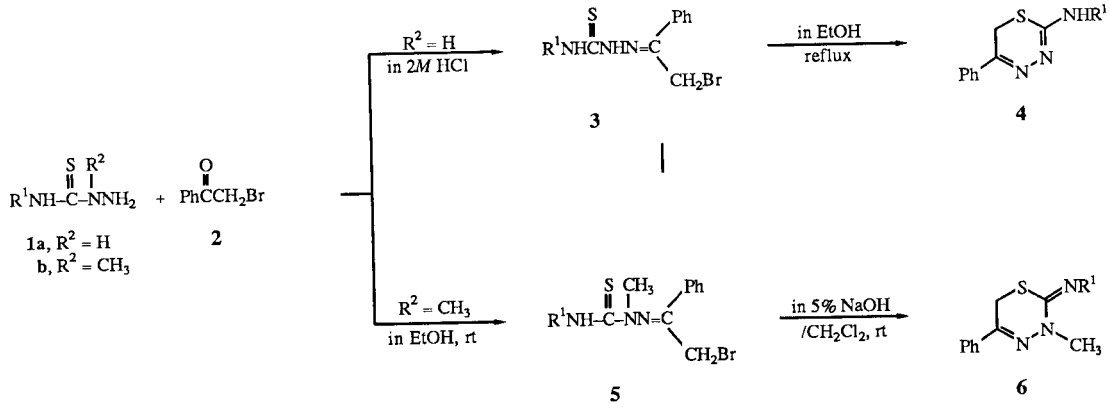
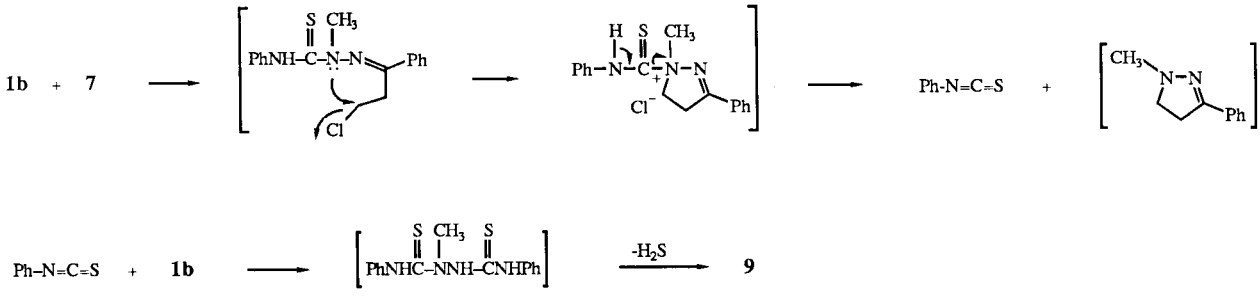


Table I

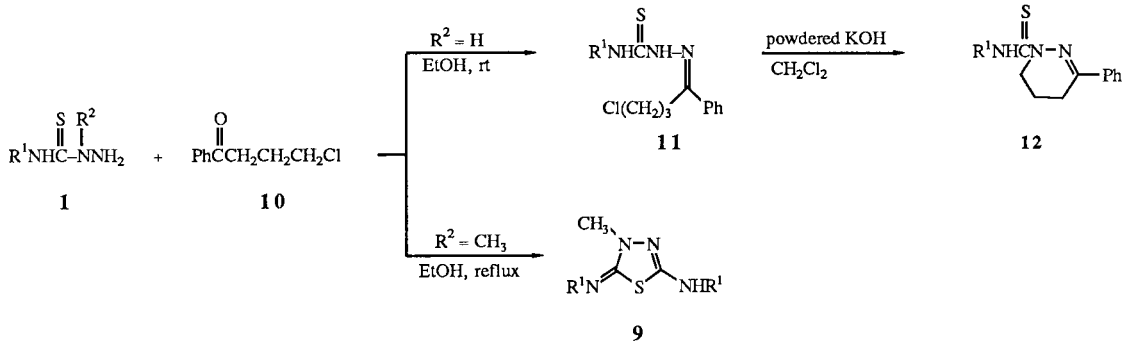
α-Bromoacetophenone 4-Substituted 2-Methylthiosemicarbazones **5** and 2-Substituted Imino-3-methyl-5-phenyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **6**

Compound No.	R^1	mp (°C)	Yield (%)	IR NH	IR (cm^{-1}) C=N	Mass (m/z)	^{1}H-NMR (δ)	Analysis (%) Calcd. (Found) C	H	N
5a	CH_3	198-199	78	2960	1585	220 (M^+–HBr)	solvent: DMSO-d_6, 3.15 (3H, s, CH_3) 3.71 (3H, s, CH_3) 4.34 (2H, s, CH_2), 7.53-7.94 (5H, m, Ph), 9.42-10.60 (1H,br, NH)	44.01 (44.49)	4.70 (4.61)	14.00 (14.15)
5b	Ph	204	83	3000	1550	281 (M^+–HBr)	solvent: DMSO-d_6, 3.75 (3H, s, CH_3) 4.12 (2H, s, CH_2), 7.04-7.99 (10H, m, Ph x 2) 8.74(1H, s, NH)	53.05 (53.15)	4.45 (4.42)	11.60 (11.82)
6a	CH_3	52-53	77	–	1590	220 (M^+)	solvent: deuteriochloroform 3.14 (3H s, CH_3), 3.52 (3H, s, CH_3), 3.76 (2H, s, CH_2) 7.26-7.95 (5H, m, Ph)	60.25 (60.54)	5.98 (5.83)	19.16 (19.11)
6b	Ph	196-197	75	–	1590	281 (M^+)	solvent: DMSO-d_6 3.73 (3H, s, CH_3) 4.10 (2H, s, CH_2), 7.0-8.0 (10H, m, Ph x 2)	68.30 (68.03)	5.37 (5.35)	14.93 (14.86)

Scheme 3



Scheme 4



cyclization occurred in an entirely different fashion. Although the reaction did not proceed at any rate under the same reaction condition as the case of the compound **8**, the unexpected product, 2,3-dihydro-1,3,4-thiadiazole **9**, was obtained in boiling ethanol containing a small amount of acetic acid in 52% yield (Scheme 2).

The reaction mechanism is presumed as follows: the terminal amino group of **1b** (R^1 = Ph) initially attacks the carbonyl group of **7** to afford the corresponding thiosemicarbazone, followed by the intramolecular cyclization between the *N*-methyl nitrogen and the chloromethylene group to the pyrazoline ring intermediate, which undergoes ready degradation to form phenyl isothiocyanate. The isothiocyanate immediately reacts with the unchang-

Table II

γ-Chlorobutyrophenone 4-Substituted Thiosemicarbazones (**11**) and 3-Phenyl-1 (4*H*)-pyridazinecarbothioamides **12**

Compound No.	R^1	mp (°C)	Yield (%)	IR NH	IR (cm^{-1}) C=N	Mass (m/z)	^{1}H-NMR (δ)	Analysis (%) Calcd. (Found) C	H	N
11a	CH_3	96-96.5	74	3300	1530	269 (M^+)	solvent: deuteriochloroform 1.73-2.08 (2H, m, CH_2), 2.93 (2H, t, CH_2, J = 6.0 Hz), 3.27 (3H, d, CH_3, J = 4.8 Hz) 3.60 (2H, t, CH_2, J = 6.0 Hz) 7.25-7.80 (5H, m, Ph) 8.19 (1H, s, NH), 8.84 (1H, s, NH)	53.42 (53.48)	5.98 (5.87)	15.58 (15.88)
11b	Ph	110-110.5	78	3200	1580	295 (M^+–HCl)	solvent: deuteriochloroform 1.77-2.39 (2H, m, CH_2), 2.62-3.17 (2H, m, CH_2), 3.62 (2H, t, CH_2, J = 6.0 Hz) 7.25-7.80 (10H, m, Ph x 2) 9.06 (1H, s, NH), 9.42 (1H, s, NH)	61.53 (61.56)	5.47 (5.47)	12.66 (12.70)
12a	CH_3	115-117	73	3310	1515	233 (M^+)	solvent: DMSO-d_6, 1.75-2.31 (2H, m, CH_2), 2.71(2H, t, CH_2, J = 6.0 Hz) 3.07 (3H, d, CH_3, J = 4.5 Hz), 4.20 (2H, t, CH_2, J = 6.0 Hz) 7.34-8.06 (5H, m, Ph) 8.60 (1H, s, NH)	61.77 (61.81)	6.48 (6.46)	18.01 (18.09)
12b	Ph	112-112.5	63	3280	1580	295 (M^+)	solvent: deuteriochloroform 1.81-2.30 (2H, m, CH_2), 2.74 (2H, t, CH_2, J = 6.0 Hz) 4.46 (2H, t, CH_2, J = 6.0 Hz) 7.20-7.90 (10H, m, Ph x 2) 9.93 (1H, s, NH)	69.12 (69.18)	5.80 (5.60)	14.23 (14.09)

ed **1b**, followed by cyclization with elimination of hydrogen sulfide to provide **9** (Scheme 3).

This assumption was supported by the result that the reaction of **1b** (R^1 = Ph) with phenyl isothiocyanate under the similar reaction condition gave **9**.

Jones *et al.* [5] have reported that the reaction of 4-methylthiosemicarbazide with γ-chlorobutyrophenone **10** in boiling propanol provided pyrrolo[1,2-*b*]triazole derivative in 41% yield. However when the same reaction was carried out in ethanol at room temperature, the corresponding thiosemicarbazone intermediates **11** were successfully isolated in 74-78% yields. The thiosemicarbazone **11** was readily cyclized to pyridazinothiocarboxamide **12** [6] by treating with potassium hydroxide in dichloromethane in the presence of a catalytic amount of the phase transfer catalyst, benzyltriethylammonium chloride, at room temperature in 63-73% yields, without being isolated any other anticipated pyrrolo[1,2-*b*]triazole. However, in the treatment of 2,4-disubstituted thiosemicarbazides **1b** and γ-butyrophenone **10** in ethanol at room temperature, the thiosemicarbazone intermediates were not isolated and instead 2,3-dihydro-1,3,4-thiadiazole **9** was obtained in one-pot in low yield (Scheme 4).

The spectral data and the elemental analyses of the compounds **11** and **12** are shown in Table II.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were recorded with a JASCO A-100 grating infrared spectrometer. The ^{1}H-nmr spectra were recorded on a JEOL 60 MHz high-resolution nmr instrument. Mass spectra were obtained on a JEOL 01SG mass spectrometer.

α-Bromoacetophenone 4-Substituted 2-Methylthiosemicarbazones **5** and 2-Substituted Imino-3-methyl-5-phenyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **6**.

A mixture of 4-substituted 2-methylthiosemicarbazide (5 mmoles) and α-bromoacetophenone (5 mmoles) in ethanol (30 ml) was stirred for 12 hours at room temperature. The resulting precipitates were collected and recrystallized from a mixture of dichloromethane and *n*-hexane to yield **5**. A solution of the compound **5** in a mixture of 5% sodium hydroxide and dichloromethane was vigorously stirred for 15 minutes at room temperature. The dichloromethane layer was separated, washed with water (30 ml x 2), dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to afford **6**. The data of **5** and **6** are summarized in Table I.

N-Substituted 3-Phenyl-2-(1*H*)-pyrazoline-1-carbothioamides **8**.

A mixture of 4-substituted thiosemicarbazide (5 mmoles), γ-chloropropiophenone (5 mmoles), and ethanol (30 ml) was stirred overnight at room temperature. The resulting precipitates were collected and recrystallized from ethanol to give **8**. The melting

points and the yield are as follows: R = H, 141-142°, 21%; R = CH_3, 139-140°, 33%; R = $PhCH_2$, 155-156°, 20%; R = Ph, 161-162°, 57%.

5-Anilino-3-methyl-2-phenylimino-2,3-dihydro-1,3,4-thiadiazole (**9**).

1) To a solution of 2-methyl-4-phenylthiosemicarbazide (5 mmoles) and γ-chloropropiophenone (5 mmoles) in ethanol (30 ml) was added a small amount of acetic acid, and the mixture was heated overnight under reflux. The resulting precipitates were collected and recrystallized from ethanol to give the hydrochloride of **9** melting at 240-244° in 52% yield.

Anal. Calcd. for $C_{15}H_{15}N_4SCl$: C, 56.51; H, 4.74; N, 17.57. Found: C, 56.86; H, 4.64; N, 17.08.

The free base had mp 175.5-176°; ir (potassium bromide): cm^{-1} 2900 (CH_3), 1610 (NH), 1590, 1525 (C=N); ^{1}H-nmr (deuteriochloroform): δ 3.61 (3H, s, CH_3), 6.30 (1H, br, NH), 6.93-7.35 (10H, m, Ph x 2); ms: (free base) 282 (M^+).

The treatment of 2-methyl-4-phenylthiosemicarbazide with γ-chlorobutyrophenone under the same reaction conditions also gave **9**.

2) A solution of 2-methyl-4-phenylthiosemicarbazide (5 mmoles) and phenylisothiocyanate (5 mmoles) in ethanol (25 ml) was refluxed for 24 hours. The solution was evaporated to dryness under reduced pressure, and the residue was recrystallized from ethanol to give **9** in 85% yield, which was identified with that obtained by the above method.

γ-Chlorobutyrophenone 4-Substituted Thiosemicarbazones **11** and 3-Phenyl-1(4*H*)-pyridazinecarbothioamide (**12**).

A mixture of 4-substituted thiosemicarbazide (5 mmoles), γ-chlorobutyrophenone (5 mmoles), and ethanol (30 ml) was stirred for 12 hours at room temperature. The resulting precipitates were collected and recrystallized from dichloromethane-*n*-hexane to give **11**. To a solution of **11** in dichloromethane (30 ml) was added a catalytic amount of benzyltriethylammonium chloride and powdered potassium hydroxide (7.5 mmoles), and the mixture was stirred for 10 minutes at room temperature. The mixture was then filtered, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. The resulting precipitates were collected and recrystallized from dichloromethane to give **12**. The data of the compounds **11** and **12** are summarized in Table I.

REFERENCES AND NOTES

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[6] The melting point of the compound **12a** (R = CH_3) agreed with that in the literature.