The Reaction of Substituted Thiosemicarbazides and γ-Haloketones

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The reactions of substituted thiosemicarbazides and γ-halobutyrophenones afforded derivatives of the tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,4]triazole-2(3*H*)-thione ring system.

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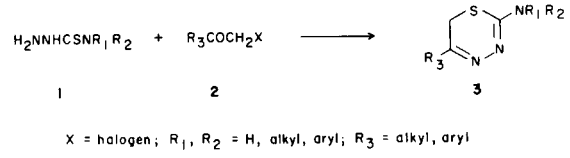
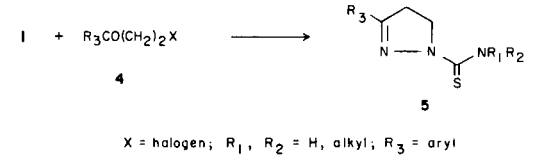
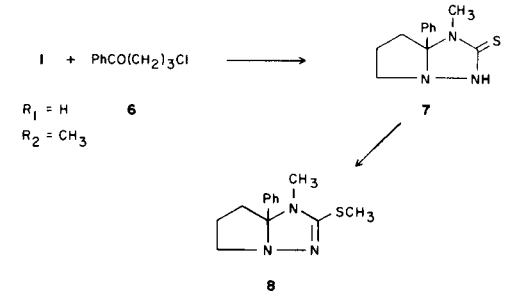
The reactions of thiosemicarbazides **1** and α-haloketones **2** are known to yield 2-amino-1,3,4-thiadiazines **3** [1].



We have recently reported that the analogous reactions of **1** and β-haloketones **4** afford pyrazoline derivatives **5** [2].

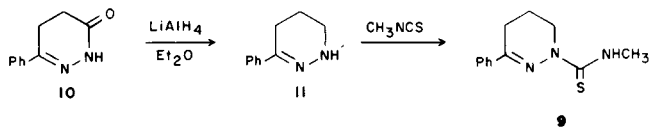


We have subsequently investigated the corresponding reactions of **1** and γ-haloketones, and have observed these cyclizations to occur in an entirely different fashion. Thus, reaction of 4-methyl-3-thiosemicarbazide (**1**, R_1 = H, R_2 = CH_3) and γ-chlorobutyrophenone (**6**) gave a complex mixture from which was isolated pyrrolo[1,2-*b*]triazole derivative **7** in 41% yield.



The structural assignment was based primarily upon consideration of the material's ^1H and ^{13}C nmr spectra. More specifically, the ^1H nmr spectrum, in addition to an aromatic absorption, exhibited resonances attributable to the following moieties: an NH, a methyl, and three methylenes. The off-resonance ^{13}C nmr spectrum supported the existence of the methyl group and the three methylenes while further indicating the presence of a quaternary carbon by a singlet resonance at 95.0 ppm. In addition, the ^{13}C nmr spectrum also exhibited a thiocarbonyl resonance at 178.2 ppm [3]. Methylation of **7** led to a loss of the thiocarbonyl absorption and the introduction of a C=N signal at 152.3 ppm indicating formation of methylthio derivative **8**.

While double cyclizations of ketones bearing proximal electrophilic centers and either 1,4- or 1,5-dinucleophiles have been observed [4], we were somewhat surprised that the reaction had not paralleled the analogous reactions of **1** and β-haloketones, and therefore expected to isolate pyridazine derivative **9**. With this in mind, the filtrate from which **7** was isolated was flash chromatographed [5] yielding trace amounts of **9**. The structure of **9** was substantiated by the presence of a doublet at δ 3.18 for the secondary methylamino moiety in the material's ^1H nmr spectrum and by the presence of thiocarbonyl and C=N resonances in the material's ^{13}C nmr spectrum. The structural assignment was further supported by the product's alternate synthesis from pyridazinone **10** [6] *via* reduction [7] and thiocarbamoylation with methyl isothiocyanate.



Formation of both **7** and **9** may be rationalized as occurring *via* thiosemicarbazone **12** which could cyclize directly to pyridazine **9**. Alternately **12** could cyclize to triazoline **13** which in a second ring-closure could yield the observed bicyclic product **7**.

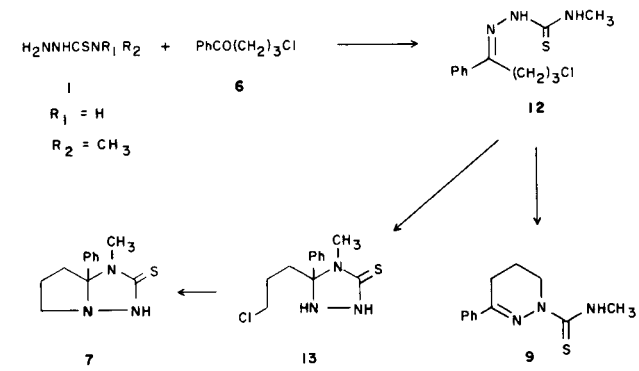
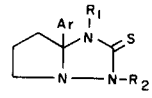


Table I

Tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,4]triazole-2(3*H*)-thiones



Compound Number	Ar	R_1	R_2	Mp °C	Crystallization Solvent [a]	Analyses % Calcd./Found C	H	N	Formula	% Yield
7	C_6H_5	CH_3	H	148-150	B	61.77	6.48	18.01	$C_{12}H_{15}N_3S$	41
						61.77	6.53	17.94		
14	C_6H_5	C_2H_5	H	126-128	B	63.12	6.93	16.99	$C_{13}H_{17}N_3S$	37
						63.00	6.95	16.92		
15	C_6H_5	C_6H_5	H	183-185	B	69.12	5.80	14.22	$C_{17}H_{17}N_3S$	10
						69.15	5.77	14.27		
16	C_6H_5	CH_3	CH_3	83-85	C	63.12	6.93	16.99	$C_{13}H_{17}N_3S$	46
						63.15	6.95	16.96		
17	4-FC_6H_4	CH_3	H	120-122	B	57.35	5.61	16.72	$C_{12}H_{14}FN_3S$	32
						57.15	5.58	16.84		
18	4-ClC_6H_4	CH_3	H	159-161	A	53.82	5.27	15.69	$C_{12}H_{14}ClN_3S$	42
						53.51	5.19	16.01		

[a] A, dichloromethane-hexane; B, ethyl acetate-hexane; C, hexane.

In order to determine the generality of this double cyclization and to provide additional examples for biological screening, several derivatives were prepared (Table I).

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. The infrared spectra were determined on a Perkin-Elmer 521 spectrometer and the nuclear magnetic resonance spectra were recorded on a Varian FT80 spectrometer. The chemical shifts are given in parts per million from tetramethylsilane as the internal standard. Peak multiplicities in the ^{13}C nmr spectra result from off-resonance decoupling procedures. Mass spectra were obtained on a Finnigan 1015 quadrupole mass spectrometer with model 3300 electronics.

7a-Phenyl-5,6,7,7a-tetrahydro-1-methyl-1*H*-pyrrolo[1,2-*b*][1,2,4]triazole-2(3*H*)-thione (**7**).

4-Methyl-3-thiosemicarbazide (4.2 g, 0.040 mole) and γ-chlorobutyrophenone (8.0 g, 0.044 mole) were heated to reflux in 2-propanol (200 ml). After being refluxed for 48 hours the solvent was evaporated leaving an oil which was dissolved in dichloromethane. The solution was transferred to a separatory funnel where it was washed in turn with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solutions. After drying over anhydrous sodium sulfate the dichloromethane was evaporated leaving a brown oil which partially crystallized. Trituration with ether and filtration gave a light yellow solid. This was purified by flash chromatography using 10% ethyl acetate-90% dichloromethane as the eluent and subsequent crystallization from ethyl acetate-hexane afforded **7** as colorless prisms, 3.8 g (41%), mp 148-150°; ^1H nmr (deuteriochloroform): δ 8.1 (broad s, 1, NH), 7.35 (s, 5, aromatic), 3.4-3.0 (m, 2, CH_2), 2.98 (s, 3, CH_3), 2.6-2.3 (m, 2, CH_2), 2.2-1.7 (m, 2, CH_2); ^{13}C nmr (deuteriochloroform): 178.2 (C=S), 139.3, 128.5, 125.7 (aromatic), 95.0 (s, C_{7a}), 59.9 (t, CH_2), 33.8 (t, CH_2), 29.3 (q, CH_3), 23.3 (t, CH_2) ppm; ir (potassium bromide): 3130 (NH) cm^{-1}; uv (ethanol): λ max = 246 nm, ε = 16,500; ms: 233 (M^+, 26). Evaporation of the ethereal filtrate from the trituration afforded an oil which was flash chromatographed using 2% ethyl acetate-98% dichloromethane as the eluent. This afforded 5,6-dihydro-*N*-methyl-3-phenyl-1(4*H*)-pyridazinecarbothioamide (**9**) as a colorless solid which crystallized from 2-propanol yielding colorless needles, 0.040 g (0.4%), mp 115-117°. This material was identical in all respects with an authentic sample prepared from pyridazinone, **10**.

General Procedure for the Preparation of Pyrrolo[1,2-*b*][1,2,4]triazoles.

The thiosemicarbazide (0.010 mole) and halobutyrophenone (0.011 mole) were heated to reflux in 2-propanol (50 ml). After being refluxed for 48 hours the solvent was evaporated leaving an oil which was dissolved in dichloromethane. After being transferred to a separatory funnel, the solution was washed in turn with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride before being dried over anhydrous sodium sulfate. Filtration of the drying agent and evaporation of the filtrate generally afforded an oil which in some instances crystallized. In those cases in which crystallization occurred, trituration with ether and filtration afforded the crude product which was purified either by crystallization alone or by a combination of flash chromatography and subsequent crystallization. In those cases in which crystallization did not occur, flash chromatography of the isolated oil afforded a solid product which could be crystallized to analytical purity.

5,6,7,7a-Tetrahydro-1-methyl-2-methylthio-7a-phenyl-1*H*-pyrrolo[1,2-*b*]-[1,2,4]triazole (**8**).

Triazole derivative **7** (9.6 g, 0.041 mole) and methyl iodide (2.9 ml, 0.046 mole) were heated to reflux in methanol (200 ml). The solution was refluxed for 24 hours, then the solvent was evaporated and the resulting oil was neutralized with saturated aqueous sodium bicarbonate. The aqueous mixture was extracted with ethyl acetate (3×). The extracts were combined and washed with saturated aqueous sodium chloride before being dried over anhydrous sodium sulfate. Filtration of the drying agent and evaporation of the filtrate gave an oil which soon crystallized yielding a beige solid. This was purified by flash chromatography using 6% methanol-94% dichloromethane as the eluent and crystallization from hexane afforded **8** as colorless prisms, 7.0 g (69%), mp 90-92°; ^1H nmr

(deuteriochloroform): δ 7.6-7.1 (m, 5, aromatic), 3.5-2.9 (m, 2, CH_2), 2.53 (s, 3, CH_3), 2.45 (s, 3, CH_3), 2.4-2.1 (m, 2, CH_2), 2.0-1.6 (m, 2, CH_2); ^{13}C nmr (deuteriochloroform): 152.3 (C=N), 141.6, 127.8, 127.4, 126.4 (aromatic), 95.1 (C_{7a}), 56.9, 33.3, 28.5, 23.8 (aliphatic), 13.4 (methylthio) ppm.

Anal. Calcd. for $C_{13}H_{17}N_3S$: C, 63.12; H, 6.93; N, 16.99. Found: C, 63.01; H, 7.06; N, 17.27.

Alternate Synthesis of 5,6-Dihydro-*N*-methyl-3-phenyl-1(4*H*)-pyridazinecarbothioamide (**9**).

To a suspension of lithium aluminum hydride (3.4 g, 0.090 mole) and dry ether (60 ml) under argon at 0° was added portionwise pyridazinone **10** (5.23 g, 0.030 mole). The cooling bath was then removed and the reaction mixture was heated to reflux. After it had refluxed for 20 hours the reaction was cooled to 0° where it was carefully quenched by the sequential addition of water (3.4 ml), 15% aqueous sodium hydroxide (3.4 ml), and water (10.2 ml). The inorganic salts were removed by filtration and washed with several portions of ether. The filtrate was dried over anhydrous sodium sulfate before being evaporated leaving unstable amine **11** as a yellow oil, 4.8 g (100%). This was immediately dissolved in ethanol (80 ml) and methyl isothiocyanate (2.4 g, 0.033 mole) was added. The reaction mixture was heated to reflux for 3 hours and then the solvent was evaporated. The resulting orange oil was purified by flash chromatography using 2% ethyl acetate-98% dichloromethane as the eluent followed by crystallization from 2-propanol affording **9** as colorless needles, 4.9 g (70%), mp 115-117°; ^1H nmr (deuteriochloroform): δ 7.97 (broad s, 1, NH), 7.7-7.2 (m, 5, aromatic), 4.4-4.2 (m, 2, CH_2), 3.18 (d, 3, CH_3), 2.64 (t, 2, CH_2), 2.2-1.8 (m, 2, CH_2); ^{13}C nmr (deuteriochloroform): 180.1 (C=S), 147.4 (C=N), 137.0, 129.5, 128.5, 125.6 (aromatic), 43.7, 31.9, 23.4, 18.3 (aliphatic) ppm; uv (methanol): λ max = 314 nm, ε = 26,400.

Anal. Calcd. for $C_{12}H_{15}N_3S$: C, 61.77; H, 6.48; N, 18.01. Found: C, 61.60; H, 6.62; N, 18.03.

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