The Reaction of 4-Alkyl-3-thiosemicarbazides with β-Haloketones

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The reactions of 4-alkyl-3-thiosemicarbazides with β-halophenones and *o*-halophenones gave 4,5-dihydro-*N*-alkyl-3-phenyl-1*H*-pyrazole-1-carbothioamides and 3-phenyl-1*H*-indazoles, respectively.

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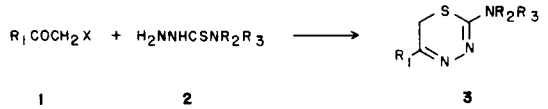
The reactions of α-haloketones **1** and thiosemicarbazides **2** are known to yield 2-amino-1,3,4-thiadiazines **3** [1].

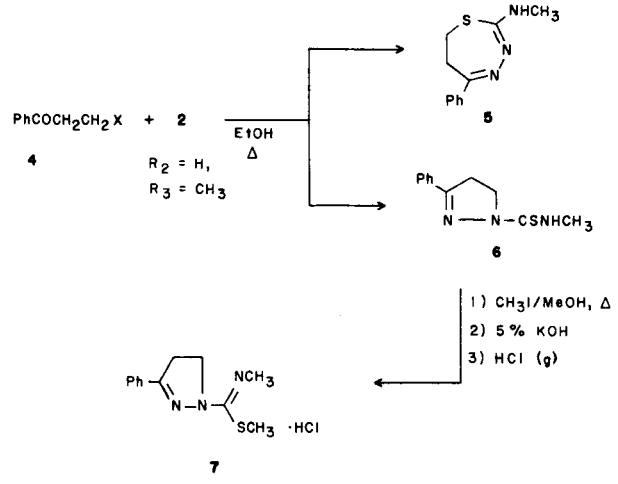


1 2 3

X = halogen; R_1 = alkyl, aryl; R_2, R_3 = H, alkyl, aryl

The analogous reactions involving β-haloketones and **2** have to the best of our knowledge not been reported. We had occasion to investigate these reactions during the course of a program directed toward the synthesis of new central nervous system agents.

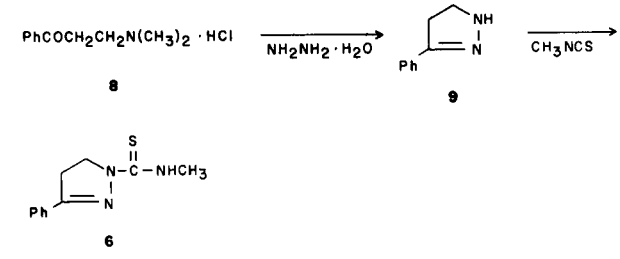
Condensation of β-chloropropiophenone **4** and 4-methyl-3-thiosemicarbazide **2** (R_2 = H, R_3 = CH_3) gave a complex reaction mixture from which was isolated a product having the empirical composition $C_{11}H_{13}N_3S$ as established by a combination of mass spectral and elemental analyses. The presence of the secondary methylamino moiety was indicated in the ^1H nmr spectrum by the presence of a doublet at δ 3.2 which collapsed to a singlet upon deuterium exchange. The structures of both the thiadiazepine **5** and pyrazoline **6** were consistent with these data.



4 5 6 7

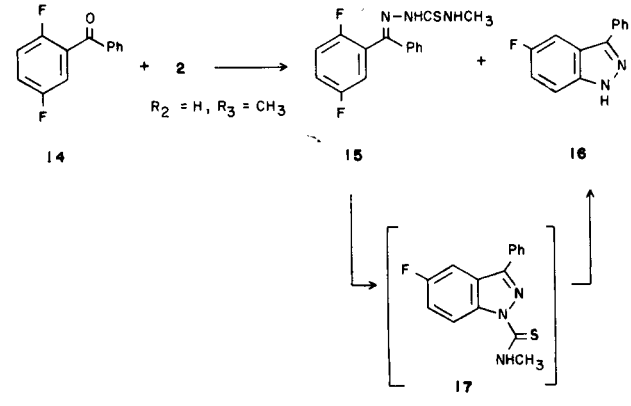
Differentiation between the two structures was accomplished by examination of the material's ^{13}C nmr spectrum which exhibited a thiocarbonyl resonance at 176.6 ppm [2] thereby excluding **5** as a potential structure. Methylation of this material led to the loss of the thiocarbonyl signal and the introduction of another C=N signal adding further support for structure **6**.

In order to further verify our structural assignment **6** was prepared by an unambiguous synthesis [3]. Reaction of Mannich base **8** with hydrazine hydrate afforded the unstable pyrazoline **9** which was immediately reacted with methyl isothiocyanate yielding **6** which was identical in all respects to that obtained from the reaction of **4** and **2** (R_2 = H, R_3 = CH_3).



8 9 6

A few representative examples prepared during the course of this study are presented in Table I.

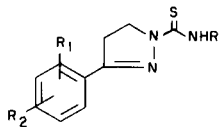


14 15 16 17

Extending the scope of the process by using an *o*-halobenzophenone derivative as the β-haloketone component gave similar results. For example, reaction of 2,5-difluorobenzophenone **14** and **2** (R_2 = H, R_3 = CH_3) gave a mixture of the thiosemicarbazone **15** and the indazole **16**. Treatment of **15** with sodium hydride in dimethylformamide gave **16** in 64% yield. Attempts to isolate the presumed thioamide intermediate **17** were unsuccessful.

Table 1

2-Pyrazoline-1-carbothioamides



Compound Number	R	R_1	R_2	Preparative Method	Mp °C	Crystallization Solvent	Analyses % Calcd./Found C	H	N	Formula	% Yield [a]
6	CH_3	H	H	A	137-139	Methanol-Water	60.24 60.17	5.97 5.57	19.16 19.51	$C_{11}H_{13}N_3S$	35
10	CH_3CH_2	H	*p*-F	A	142-143	Ethanol	57.35 57.41	5.61 5.62	16.72 16.97	$C_{12}H_{15}N_3S$	28
11	CH_3	*o*-OH	*m*-CH_3	A	226.5-228	2-Propanol	57.81 57.76	6.06 6.15	16.85 16.98	$C_{12}H_{15}N_3OS$	19
12	$(CH_3)_2CH$	H	*p*-F	B	172-174	Ethanol	58.84 58.68	6.08 6.03	15.84 15.85	$C_{13}H_{16}FN_3S$	40
13	$(CH_3)_2CH$	H	*p*-Cl	B	174-176	2-Propanol	55.41 55.20	5.72 5.76	14.91 14.93	$C_{13}H_{16}ClN_3S$	37

[a] Overall yield.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. The infrared and ultraviolet spectra were obtained using Perkin-Elmer 521 and 350 recording spectrophotometers respectively. The nuclear magnetic resonance spectra were recorded on Varian A60 and FT-80A spectrometers. The chemical shifts are given in parts per million from tetramethylsilane as the internal reference standard. Mass spectra were obtained on a Finnigan 1015 quadrupole mass spectrometer with model 3300 electronics. All spectra were consistent with the proposed structures.

Representative Procedures for the Preparation of 4,5-Dihydro-1*H*-pyrazole-1-carbothioamides.

Method A.

4,5-Dihydro-*N*-methyl-3-phenyl-1*H*-pyrazole-1-carbothioamide (**6**).

4-Methyl-3-thiosemicarbazide (2.5 g, 0.025 mole) and β-chloropropiophenone (4.2 g, 0.025 mole) were stirred under reflux in 150 ml of 2-propanol for 4 hours then concentrated *in vacuo* giving a reddish colored oil. Trituration in a small quantity of dry ether gave 1.9 g (35%) of a light brown solid. Recrystallization from methanol-water gave light brown needles of **6**, mp 137-139°; ^{1}H nmr (deuteriochloroform): δ 7.8-7.5 (m, 2H, aromatic), 7.5-7.1 (m, 4H, aromatic, NH), 4.5-4.2 (m, 2H, 5-CH_2), 3.4-3.0 (m, 2H, 4-CH_2), 3.2 (d, 3H, J = 4.8 Hz, CH_3); ^{1}H nmr (deuterium oxide, deuteriochloroform): the doublet at 3.2 coalesces to a singlet after 1 hour; ^{13}C nmr (deuteriochloroform): 176.6 (C=S), 156.1 (C=N), 131.0, 130.5, 128.7, 126.6 (aromatic), 48.5, 31.8, 31.4 (aliphatic); ir (7% chloroform): 3395 cm^{-1} (sharp singlet, NH); uv (ethanol): λ max = 325 nm, ε = 27,300; ms: 219 (M^+, 47).

Method B.

3-(4-Chlorophenyl)-4,5-dihydro-*N*-isopropyl-1*H*-pyrazole-1-carbothioamide (**13**).

3-(4-Chlorophenyl)pyrazoline (8.85 g, 0.049 mole) [4,5] and isopropylisothiocyanate (5.50 g, 0.054 mole) were stirred under reflux in 50 ml of ethanol for 3 hours. The reaction mixture upon cooling to room temperature deposited a yellow powder 6.8 g (49%). Flash chromatography [6] eluting with 1.5% ethyl acetate-methylene chloride gave an almost colorless solid 5.9 g (43%) which on crystallizatiion from 2-propanol gave pale yellow matted needles of **13**, mp 174-176°.

Methyl 4,5-Dihydro-*N*-methyl-3-phenyl-1*H*-pyrazole-1-carboximidothioate Monohydrochloride (**7**).

Compound **6** (2.19 g, 0.01 mole) and 10 ml of methyl iodide were heated and stirred in 125 ml of methanol at reflux overnight. The resulting yellow solution was allowed to cool to room temperature then concentrated on the rotary evaporator. The residual yellow oil was dissolved in methylene chloride and extracted with 5% potassium hydroxide then washed with brine. The methylene chloride layer was separated, dried (magnesium sulfate) and filtered. The filtrate was concentrated on the rotary evaporator and the residue was dissolved in dry ether. Addition of hydrogen chloride in methanol precipitated a white solid. Recrystallization of the solid from methanol-ethyl acetate gave 1.82 g (67%) of **7**, mp 157-158°; ^{1}H nmr (deuteriochloroform): δ 11 (broad s, 1H, NHCl), 7.9-7.6 (m, 2H, aromatic), 7.5-7.3 (m, 3H, aromatic), 4.6 (t, 2H, 5-CH_2), 3.6-3.2 (m, 5H, 4-CH_2 and NCH_3), 2.8 (s, 3H, SCH_3); free base ^{13}C nmr (deuteriochloroform): 154.3, 151.8 (C=N), 132.3, 129.0, 128.3, 125.8 (aromatic), 48.0, 38.3, 31.0, 16.5 (aliphatic).

2,5-Difluorobenzophenone (**14**).

Aluminum chloride (400 g, 3.00 mole) was added portionwise to a stirred solution of benzoyl chloride (116 ml, 1.00 mole) and 1,4-difluorobenzene (140 ml, 1.36 mole) at room temperature. The mixture was slowly warmed to reflux. After 6 hours the reaction mixture was carefully poured onto crushed ice. After the ice had melted the mixture was transferred to a separatory funnel and the aqueous mixture was extracted thoroughly with ether. The ethereal extract was washed in turn with saturated aqueous sodium bicarbonate and brine then dried over anhydrous sodium sulfate. Filtration and evaporation gave an orange oil. The oil was distilled at 120-123° (0.35 mm) affording **14** as a clear colorless oil, 131 g (60%).

Anal. Calcd. for $C_{13}H_8F_2O$: C, 71.56; H, 3.70. Found: C, 71.65; H, 3.77.

N_2-[(2,5-Difluorophenyl)phenylmethylene]-*N*-methylhydrazinecarbothioamide (**15**).

Potassium carbonate (3.30 g, 0.024 mole), 4-methyl-3-thiosemicarbazide (2.63 g, 0.024 mole) and **14** (5.23 g, 0.024 mole) were heated and stirred under reflux in 200 ml of methanol for 48 hours. The resulting yellow solution was allowed to cool to room temperature then concentrated to a yellow foam on the rotary evaporator. The residue was partitioned between methylene chloride and water. The methylene chloride layer was separated and dried (magnesium sulfate). The methylene chloride solution was filtered and the filtrate concentrated to a yellow oil. Flash

chromatography on silica gel eluting with 15% ethyl acetate-85% hexane gave 3.82 g (51%) of **15**, mp 153-155°; ^{1}H nmr (deuteriochloroform): δ 8.4 (s, 1H), 7.7-6.75 (m, 9H), 3.3 (d, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{13}F_2N_3S$: C, 59.00; H, 4.29; N, 13.76. Found: C, 59.26; H, 4.35; N, 13.59.

5-Fluoro-3-phenyl-1*H*-indazole (**16**).

Compound **15** (3.50 g, 0.011 mole) and a 50% dispersion of sodium hydride in mineral oil (1.06 g, 0.023 mole) were heated and stirred in 90 ml dry dimethylformamide under argon for 4-1/2 hours. The reaction mixture was neutralized to *p*H 8 with glacial acetic acid and then partitioned between methylene chloride and water. The methylene chloride was separated, dried over magnesium sulfate and filtered. The filtrate was concentrated to a yellow oil on the rotary evaporator. Flash chromatography on silica gel eluting with 15% ethyl acetate-85% hexane gave 2.0 g of slightly yellow solid, mp 95-100°. One recrystallization from cyclohexane gave 1.57 g (64%) of **16** as colorless plates, mp 125-126°; ^{1}H nmr (deuteriochloroform): δ 11.2 (broad s, 1H, NH), 8.0-7.7 (m, 2H, aromatic), 7.7-7.3 (m, 4H, aromatic), 7.3-7.0 (m, 2H, aromatic).

Anal. Calcd. for $C_{13}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.64; H, 4.49; N, 13.28.

Acknowledgement.

We thank Dr. Dave Gustafson for assistance with the ^{1}H nmr.

REFERENCES AND NOTES

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[5] See S. G. Beech, J. H. Turnball and W. Wilson, *J. Chem. Soc.*, 4686 (1952) for a general synthesis of Δ^2-pyrazolines.

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