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Heterocyclization of 1-alkyl-2-thiobiureas with α-haloketones

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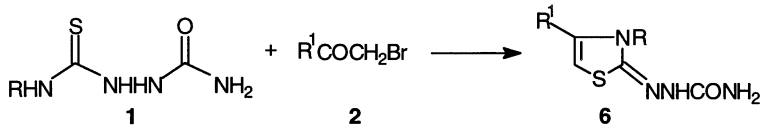
Abstract—1-Alkyl-2-thiobiureas on reaction with α-haloketones such as *p*-methoxyphenacyl bromide, *p*-methylphenacyl bromide, *p*-chlorophenacyl bromide and phenacyl bromide, were found to afford semicarbazonothiazolines in good yields.

The Hantzsch thiazole synthesis using the condensation of α-haloketones with thiourea was established long ago.[1] In subsequent research α-dihaloketones were also found to react with thiourea and yield 2-aminothiazoles.[2] However the reactions of haloketones with 2,4- and 4-substituted thiosemicarbazides are known to proceed through different modes of heterocyclization on varying the chain length between the carbonyl group and the halogen atom.[3–6] Similar results were reported with their 2,4-disubstituted counterparts.[7] The present communication describes the reactions of 1-alkyl-2-thiobiureas, which contain a thiosemicarbazide group, with α-haloketones yielding a thiazole derivative (Scheme 1).

The reaction of the 1-alkyl-2-thiobiurea **1** (R = Me; **1a**) with the α-haloketone **2** ($R^1 = p$-$MeOC_6H_4$; **2a**) in acetone at 75°C yielded a white solid after 20 min; which, on dissolution in hot water, followed by neutralization with liquor ammonia, afforded the 3-alkyl-4-substituted-2-semicarbazono-Δ^4-thiazoline **6** (**6a**, 3-methyl-4-*p*-methoxyphenyl-2-semicarbazono-Δ^4-thiazoline). The fact that the product did not undergo dehydrosulphurization with hot sodium plumbite solution indicated the absence of any –NH–C(=S)–NH or =N–C(=S)–NH_2 grouping. Reactions of **2b** (R = *p*-MeC_6H_4), **2c** (R = *p*-ClC_6H_4) and **2d** (R = C_6H_5) with 1-alkyl-2-thiobiureas gave the related 3-alkyl-4-substituted-2-semicarbazono-Δ^4-thiazolines **6** in good yields. The results are listed in Table 1. A suitable mechanism for the formation of **6** is depicted in Scheme 2. The nucleophilic thiol sulfur atom initially attacks the sp^3 carbon of the α-haloketones to form a *S*-phenacylated open chain derivative **3**. Attempts to isolate *S*-phenacylated open chain derivatives did not succeed even under mild reaction conditions as they readily undergo in situ cyclization yielding **6**. Here the +I effect of the alkyl group enhances the basic nature of nitrogen atom at position one, thereby allowing a facile nucleophilic attack on the carbonyl carbon with the elimination of water. Microanalytical and mass spectral data of the

Table 1. 3-Alkyl-4-substituted-2-semicarbazono-Δ^4-thiazolines

Entry	R	R^1	Product (yield, %)	Mp (°C)
1	Me	*p*-$MeOC_6H_4$	**6a** (80)	214
2	*i*-Pr	*p*-$MeOC_6H_4$	**6b** (74)	180
3	Pr	*p*-MeC_6H_4	**6c** (79)	200
4	Bu	*p*-MeC_6H_4	**6d** (77)	169
5	Et	*p*-ClC_6H_4	**6e** (79)	221
6	Bu	*p*-ClC_6H_4	**6f** (79)	177
7	Me	Ph	**6g** (76)	193
8	Pr	Ph	**6h** (74)	203



1 2 6

Scheme 1. **1**, R:a = Me, b = Et, c = Pr, d = *i*-Pr, e = Bu. **2**, R^1: a = *p*-$MeOC_6H_4$, b = *p*-MeC_6H_4, c = *p*-ClC_6H_4, d = C_6H_5.

Keywords: basicity; thiazolines; X-ray crystallography.

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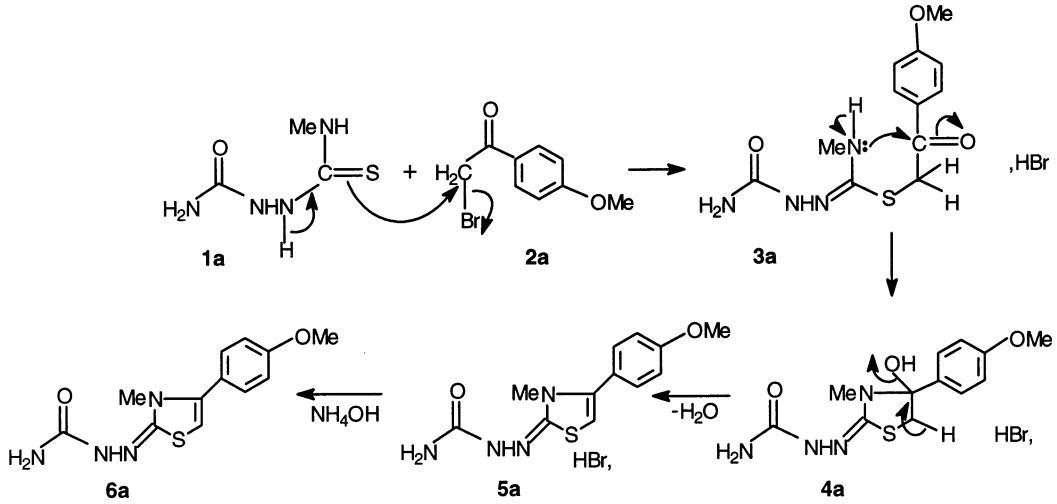

Scheme 2.

free bases indicated heterocyclic compounds of the type **6**. The proposed structure of **6a** was unambiguously proven by X-ray analysis (Fig. 1). The present communication highlights the formation of a five-membered heterocycle from an extended urea-like chain compound through *S*-alkylation.

Experimental

Representative procedure for compounds 6(a–h)

A suspension of **1a** (1.48 g, 0.01 mol) in acetone (15 ml) was refluxed with **2a** (2.29 g, 0.01 mol) at 75°C for 25 min. The resulting white product was collected and washed with diethyl ether. Neutralization of its aqueous solution with ammonia afforded **6a** and recrystallization from hot absolute ethanol gave analytically pure product. Compounds **1(a–e)** undergo similar cyclocondensation with **2b**, **2c** and **2d**.

X-ray structural analysis of compound 6a. Crystal data $C_{12}H_{14}N_4O_2S$, M = 278.33, triclinic, $P\bar{1}$, $a = 7.169$ (3), $b = 9.877$ (11), $c = 10.147$ (6) Å, $\alpha = 87.31$ (7), $\beta = 79.41$ (4), $\gamma = 73.31$ (4)°, $B = 676.5$ (9) Å^3, $Z = 2$, $D_c = 1.366$ mg m^{-3}, μ (Mo Kα) = 0.243 mm^{-1}, F (000) = 292. 2375 (2375) independent reflections were measured on an Enraf–Nonius CAD4 Diffractometer with Mo Kα radiation using ω scans. The final wR (F_2) was 0.1035 and $R1 = 0.0410$ (all data). The structure was solved using direct methods and refined by full-matrix least squares on F^2. Further details of the crystal structure investigation have been deposited at the Cambridge Crystallographic Data Centre. CCDC 147199.

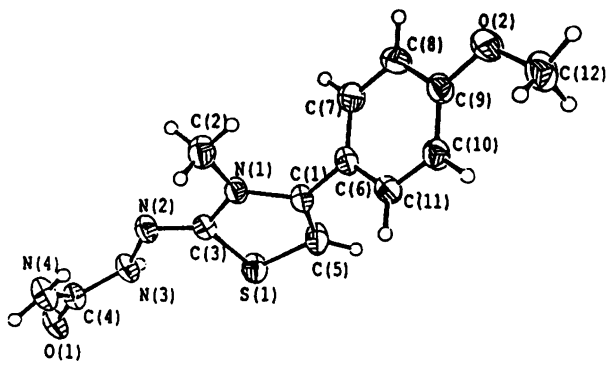

Figure 1. Ortep diagram of compound **6a** with crystallographic numbering system.

3-Methyl-4-*p*-methoxyphenyl-2-semicarbazono-Δ^4-thiazoline (6a). Yellow needles. IR (KBr, pellet): 3450, 3400, 3050, 2950, 1690, 1540, 1500, 1480, 1440, 840 cm^{-1}. ^{1}H NMR (300 MHz): 3.10 (s, 3H, NMe), 3.77 (s, 3H, PhOMe), 6.01 (s, 2H, NH_2), 6.11 (s, 1H, NH), 6.94 (d, $J = 9$ Hz, 2H, Ph), 7.39 (d, $J = 8.8$ Hz, 2H, Ph), 8.35 (s, 1H, =CH). ^{13}C NMR (300 MHz): 32.4, 55.5, 127.9, 128.9, 130.09, 131.8, 134.9, 140.8, 159.4, 163.8. MS: 278 (M$^+$, 79), 205 (28), 190 (14), 164 (22), 132 (100). Anal. Calcd. for $C_{12}H_{14}N_4O_2S$: C, 51.79; H, 5.04; N, 20.14; S, 11.51. Found: C, 51.8; H, 5.14; N, 20.16; S, 11.15

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