Heterocycles by α-Thioamidoalkylation of Unsaturated Compounds. Part VI[1]. 6*H*-1,3,5-Oxathiazines

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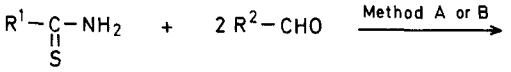
We wish to report that 6*H*-1,3,5-oxathiazines, a new class[2,3] of heterocyclic compounds, can be easily obtained by α-thioamidoalkylation of aliphatic aldehydes. This is the first time[2] that aldehydes have been shown to be versatile substrates for this type of reaction.

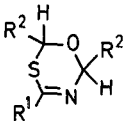
Two different experimental procedures gave satisfactory results:

Method A consists of adding at room temperature a solution of 100% sulfuric acid in acetic acid to a solution or a suspension of thioamide (1 mol) and aliphatic aldehyde (2 mol) in acetic acid. Alkaline hydrolysis gives the 6*H*-1,3,5-oxathiazine (**1**); (Scheme **A** and Table 1).

Method B, the alternative procedure, consists of adding boron trifluoride etherate complex at room temperature to a solution or a suspension of thioamide (1 mol) and aliphatic aldehyde (2 mol) in chloroform. (Scheme **A** and Table 1).

No effort was made to optimize the yields reported in Table 1.





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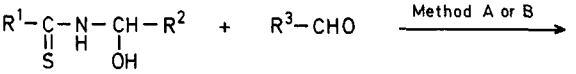
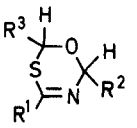
Scheme **A**

In the case $R^2 \neq H$ a couple of diastereoisomeric oxathiazines can be formed. We had evidence of this in the synthesis of compound (**1c**).

6*H*-1,3,5-Oxathiazines, in which substituents in positions 2 and 6 of the ring are different (e.g.; Scheme **B**), can be prepared by reacting the performed adduct between thioamide (1 mol) and aldehyde (1 mol), the *N*-hydroxyalkylthioamide, and the desired aldehyde (Scheme **B** and Table 1).





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Scheme **B**

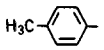
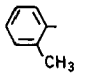
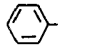
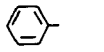
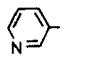
According to this procedure oxathiazines (**2**; $R^2 = H$) were synthesized by reacting *N*-hydroxymethylthioamides with aliphatic aldehydes.

This means that also in the case in which thioamide (1 mol) reacts with aldehyde (2 mol), one mol of aldehyde is consumed (*in situ*) in the condensation with thioamide, while the other acts as substrate of α-thioamidoalkylation reaction.

In the reaction with formaldehyde itself (**1b**, Table 1) better yields were obtained using *N*-hydroxymethylthioamides instead of the α-thioamidomethylating agents, thioamides plus formaldehyde.

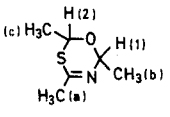
The structures assigned to compounds **1a–c**, **2a–c** (Table 1) follow from the available N.M.R., I.R., Mass[4] spectral data (Table 2).

Table 1. Preparation of 6*H*-1,3,5-oxathiazines **1** and **2**

Product	R^1	R^2	R^3	Yield (%)	M.p.[a]	Method	Reaction time
1a		H_3C	–	91[b]	32–34°	B[c]	2 h
1b		H	–	38	45–46°	A[c]	24 h
1c	H_3C	H_3C	–	78	oil[d]	A[c]	2 h
2a		H	H_3C	77[f]	oil	A[g]	2 h
2b		H	C_2H_5	77[f]	oil	A[g]	2 h
2c		H	CH_3	38	30–32°	A[c]	2 h

[a] Melting points were determined by the Kofler method and were not corrected.
[b] No evidence of the presence of diastereoisomers.
[c] The synthesis is reported in experimental part.
[d] Mixture of two diastereoisomers. Yield of the product isolated according to the procedure used in the preparation of compound **1a**.
[e] The reaction between thioacetamide (0.03 mol) and acetaldehyde (0.06 mol) in acetic acid (45 ml) and in the presence of 100% sulfuric acid (0.03 mol), was carried out according to procedure described in the synthesis of **1b**.
[f] Yield of the pure product isolated via chromatography on silica.
[g] The experimental procedure followed is identical to that described in the synthesis of **1b**.

Table 2[a,b]. ^{1}H-N.M.R.[c] and Mass Spectral Data for Products **1a–c** and **2a–c**

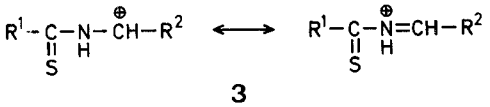
Product	^{1}H-N.M.R. δ ppm	Mass Spectra *m/e* ($M^{\oplus}$)
1a	1.56 (d, 3H, J_{H,CH_3} = 6.1 Hz), 1.58 (d, 3H, J_{H,CH_3} = 6.1 Hz), 5.20 (q, 1H), 5.29 (q, 1H)	221
1b	5.10 (s, 2H), 5.40 (s, 2H)	193
1c[d]	1.49 (d, 3H), 1.51 (d, 3H, $J_{H(1),CH_3(b)} = J_{H(2),CH_3(c)}$ = 6.2 Hz), 2.11 [d, CH_3(a)], 5.03 [m, H(1), $J_{CH_3(a),H(1)}$ = 1.8 Hz], 5.19 [q, H(2)]	145
	1.44 (d, 3H), 1.52 (d, 3H), $J_{H(1),CH_3(b)} = J_{H(2),CH_3(c)}$ = 5.8 Hz), 2.12 [d, CH_3^a(a), $J_{H(1),CH_3(a)}$ = 1.4 Hz], 5.40 [m, H(1)]	
2a	1.52 (d, 3H), 5.15 (q, 1H, J_{H,CH_3} = 5.9 Hz), [5.33 (1H), 5.68 (1H)] (ABq), $J_{H,H}$ = 14.9 Hz	193
2b	4.84 (t, 1H, $J_{CH_2,H}$ = 3.69 Hz), [5.21 (1H), 5.55 (1H)] (ABq), $J_{H,H}$ = 14.62 Hz	205
2c	1.60 (d, 3H), 5.22 (q, 1H, J_{H,CH_3} = 5.85 Hz), [5.39 (1H), 5.66 (1H)], (ABq), $J_{H,H}$ = 15.07 Hz	194

[a] Satisfactory analytical data were obtained for all compounds.
[b] In the I.R. spectra the —C=N stretching for all compounds gives a strong band at 6.10–6.25 μ; no bands in the N—H, O—H stretching region. Spectra were recorded with a Perkin-Elmer 137 spectrophotometer.
[c] Solvent: $CDCl_3$; internal standard: TMS.
Spectra of compounds **1a** and **1c** were recorded with a Bruker WH-90 instrument while those of compounds **1b**, **2a–c** were recorded with a Jeol C-60 HL instrument.
[d] The data were determined on diastereoisomers mixture.

Generally 6*H*-1,3,5-oxathiazines are stable under aqueous basic conditions at room temperature, while they decompose to the starting reagents under aqueous acidic conditions.

Generally 6*H*-1,3,5-oxathiazines are temperature labile. They can be stored at −20°, but cannot be purified by distillation in vacuum without avoiding decomposition[5] in some degree.

On the basis of our experience[1], the most likely reaction scheme involves a polar 1,4-cycloaddition[6] of thioamidoalkyl ions (**3**) to aldehydes.



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Further work is in progress[5] to extend the scope of the reaction and to clarify the reaction mechanism.

Preparation of *N*-(Hydroxymethyl)thioamides:

The *N*-(hydroxymethyl)thioamides were prepared according to the method of Böhme and Hotzel[7]. The 2-methylphenyl and 3-pyridyl derivatives had not been described by these authors. *N*-(hy-

droxymethyl)-thionicotinamide (m.p. 123–125°) and *N*-(hydroxymethyl)-2-methylthiobenzamide (oil) were synthesized from thionicotinamide (0.2 mol), 40% aqueous formaldehyde (5.33 mol), and water (as solvent) (1.5 l) and from 2-methylthiobenzamide (0.1 mol), 40% aqueous formaldehyde (3.1 mol), and water (as solvent) (1.2 l), respectively.

2,6-Dimethyl-4-(4-methylphenyl)-6*H*-1,3,5-oxathiazine (1a):
To a stirred mixture of 4-methylthiobenzamide (8.55 g, 0.05 mol) and of acetaldehyde (4.40 g, 0.1 mol) in chloroform (50 ml), kept at 0–5°, boron-trifluoride etherate (12.5 ml, d = 1.13, 0.1 mol) was added in 5 min. The solution was kept for 2 h at 15°. The reaction mixture was poured into a saturated sodium carbonate solution (150 ml) and extracted with diethyl ether (3 × 150 ml). The solvent was distilled in vacuum. The residue on treatment with petroleum ether (40–60°), left an insoluble product. Active charcoal was added to this suspension, which was than filtered through a paper filter. The solvent was distilled in vacuum and the residue was crystallized (at −70°) from *n*-hexane to give **1a**; yield: 10.1 g (91%) as analytically pure product; m.p. 32–34°.

$C_{12}H_{15}NOS$	calc.	C 64.49	H 7.17	N 6.17	S 14.48
(221.31)	found	64.60	7.37	6.32	14.20

4-(2-Methylphenyl)-6*H*-1,3,5-oxathiazine (1b):
To a stirred mixture of 2-methyl-*N*-(hydroxymethyl)-thiobenzamide (5.43 g, 0.03 mol) and 1,3,5-trioxane (0.9 g; 0.03 mol of formaldehyde) in acetic acid (30 ml), kept at 15°, a solution of 100% sulfuric acid (2.94 g, 0.03 mol) in acetic acid (15 ml) was added. The solution was kept for 24 h at 15°. The reaction mixture was poured into crushed ice and made alkaline with a saturated sodium carbonate solution and extracted in diethyl ether (3 × 150 ml). The solvent was distilled in vacuum. Chromatography of residue on silica using petroleum ether (40–60)/diethyl ether (95:5) as eluent gave **1b**; yield: 2.9 g. Crystallization from *n*-hexane at −20° gave **1b** as an analytically pure product; yield: 2.2 g (38%); m.p. 45–46°.

$C_{10}H_{11}NOS$	calc.	C 62.14	H 5.74	N 7.25	S 16.59
(193.26)	found	62.33	5.56	7.29	16.58

2-Methyl-4-(3-pyridyl)-6*H*-1,3,5-oxathiazine (2c):
To a stirred mixture of *N*-hydroxymethylthionicotinamide (5.04 g, 0.03 mol) and acetaldehyde (1.32 g, 0.03 mol) in acetic acid (30 ml), kept at 15°, a solution of 100% sulfuric acid (5.88 g, 0.06 mol) in acetic acid (15 ml) was added. The solution was kept for 2 h at 15°. The reaction mixture was poured into crushed ice and made alkaline with a saturated sodium carbonate solution and extracted in dichloromethane (3 × 100 ml). The solvent was distilled in vacuum. Chromatography of residue on silica using petroleum ether (40–60°)/diethyl ether (70:30) gave **2c**; yield: 2.5 g. Crystallization from *n*-hexane at −20° gave **2c** as an analytically pure product; yield: 2.2 (38%); m.p. 30–32.

$C_9H_{10}N_2OS$	calc.	C 55.64	H 5.18	N 14.42	S 16.50
(194.25)	found	55.44	5.28	14.31	16.70

Received: August 7, 1975

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