α-Thioamidoalkylation of Aldehydes. A General Route to 6*H*-1,3,5-Oxathiazines

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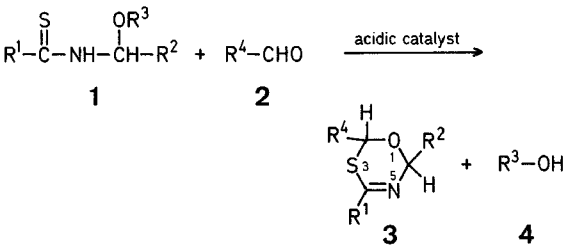
We recently reported that 6*H*-1,3,5-oxathiazines can be obtained from *N*-(hydroxymethyl)-thioamides or thioamides and aliphatic aldehydes[1,2]. So far, α-thioamidoalkylation of aldehydes was a synthetic method restricted to the preparation of 2-alkyl-4-alkyl(or aryl) and 2,6-dialkyl(identical alkyl)-4-aryl-6*H*-1,3,5-oxathiazines. The aim of the present work is to show that this method represents a general route to 6*H*-1,3,5-oxathiazines (**3**) having a large variety of substituents in the 2, 4, and 6 positions.

The synthesis of the new oxathiazines (**3**) was possible thanks to the availability of new α-thioamidoalkylating agents[3] as well as to the choice of particular experimental conditions.

We report here the reactions of *N*-(1-alkoxyalkyl)-[3] (**1**; R^1, R^2 = alkyl, aryl; R^3 = alkyl) or *N*-(1-hydroxy-2,2,2-trichloroethyl)-thiocarboxamides[4] (**1**; R^1 = alkyl, aryl; $R^2 = CCl_3$; R^3 = H) with aldehydes (**2**; R^4 = alkyl, aryl) and the reaction of *N*-(hydroxymethyl)-thiocarboxamides[5,6] (**1**; R^1 = alkyl, aryl; $R^2 = R^3$ = H) with aromatic aldehydes (**2**; R^4 = aryl).



To our knowledge, this method for the synthesis of 6*H*-1,3,5-oxathiazines is new and the products obtained have hitherto not been described.

2,4,6-Trisubstituted-6*H*-1,3,5-oxathiazines were prepared by reaction of *N*-(1-alkoxyalkyl)- or *N*-(1-hydroxy-2,2,2-trichloroethyl)-thiocarboxamides with aliphatic or aromatic aldehydes in chloroform at room temperature in the presence of boron trifluoride etherate as acidic catalyst (Method A).

2,4-Diaryl-6-trichloromethyl-6*H*-1,3,5-oxathiazines were obtained in nearly quantitative yield by using methanesulfonic acid as solvent and as catalyst (Method B).

Attempts to synthesize 2,4-diaryl-6*H*-1,3,5-oxathiazines from *N*-(hydroxymethyl)-thiocarboxamides and aromatic aldehydes under the conditions of Methods A or B lead to poor or no results. These compounds may be obtained in good yields, however, by carrying out the reaction in the presence of strongly acidic catalysts at low temperatures at which the reaction rates are still sufficient and the stability of the products is enhanced, e.g., in liquid sulfur dioxide at −20° in the presence of methanesulfonic acid (Method C). The use of stronger acidic catalysts such as trifluoromethanesulfonic acid, fluorosulfonic acid, and fluorosulfonic acid-antimony(V) fluoride gives similar results.

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Table 1. Preparation of 6*H*-1,3,5-oxathiazines (**3**)

R^1	R^2	R^3	R^4	Method	Reaction time [h]	Products	Yield[a] [%]	Ratio[b] **3**:**3'**	m.p. (solvent) **3**	m.p. (solvent) **3'**	Molecular formula[c]
4-Cl C_6H_4	H	H	4-Cl C_6H_4	C	2	**3a**	70	—	135° (acetonitrile)		$C_{15}H_{11}Cl_2NOS$ (324.2)
4-Cl C_6H_4	H	H	4-H_3C C_6H_4	C	2	**3b**	65	—	101° (acetonitrile)		$C_{16}H_{14}ClNOS$ (303.8)
4-Cl C_6H_4	CCl_3	H	4-O_2N C_6H_4	B	24	**3c** + **3c'**	91	3	118–119° (aceto-nitrile)	147–148° (aceto-nitrile)	$C_{16}H_{10}Cl_4N_2O_3S$ (452.1)
4-Cl C_6H_4	CCl_3	H	4-H_3C C_6H_4	B	24	**3d** + **3d'**	85	17		131–133° (methanol)	$C_{17}H_{13}Cl_4NOS$ (421.2)
4-Cl C_6H_4	CCl_3	H	4-Cl C_6H_4	B A	24 24	**3e** + **3e'**	92 30	12		119–120° (aceto-nitrile)	$C_{16}H_{10}Cl_5NOS$ (441.6)
4-H_3C C_6H_4	CCl_3	H	CH_3	A	0.30	**3f** + **3f'**	46	5	82–84° (PE −20°)	105–107° (PE −20°)	$C_{12}H_{12}Cl_3NOS$ (324.7)
4-Cl C_6H_4	C_6H_5	CH_3	CH_3	A	0.50	**3g** + **3g'**	81	3	94–96° (aceto-nitrile)	116–117° (n-hexane)	$C_{16}H_{14}ClNOS$ (303.8)
CH_3	C_6H_5	CH_3	CH_3	A	0.25	**3h** + **3h'**	43	5	oil	oil	$C_{11}H_{13}NOS$ (207.3)
4-Cl C_6H_4	CH_3	C_2H_5	C_2H_5	A	0.25	**3i** + **3i'**	95	[d]	oil		$C_{12}H_{14}ClNOS$ (255.8)
4-Cl C_6H_4	C_2H_5	C_2H_5	CH_3	A	0.50	**3j** + **3j'**	91	[d]	oil		$C_{12}H_{14}ClNOS$ (255.8)

[a] Yields (based on introduced **1**) of products isolated by chromatography on silica gel.
[b] Determined by ^{1}H-N.M.R. analysis of crude reaction mixture.
[c] All products **3** and **3'** gave satisfactory microanalyses: C, ±0.15; H, ±0.15; N, ±0.10; S, ±0.22.
[d] One isomer is preponderant; the ratio of the diastereoisomers is difficult to determine. Products are free from any other oxathiazine.

Table 2. ^{1}H-N.M.R. Data of Representative Compounds **3**

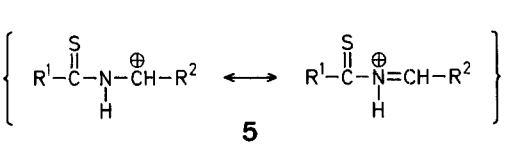
Compound	^{1}H-N.M.R. ($CDCl_3$) TMS δ [ppm]
3a	5.64, 5.90 (ABq, 1H + 1H, J = 16.5 Hz); 6.1 (s, 1H)
3e	5.65 (s, 1H); 6.57 (s, 1H)
3e'	6.00 (s, 1H); 6.35 (s, 1H)
3f	1.68 (d, 3H, J = 6.2 Hz); 2.39 (s, 3H); 5.35 (q, 1H, J = 6 Hz); 5.68 (s, 1H)
3f'	2.39 (s, 3H); 1.73 (d, 3H, J = 6.5 Hz); 5.61 (q, 1H, J = 6.5 Hz); 5.64 (s, 1H)
3g	1.50 (d, 3H, J = 6.0 Hz); 4.90 (q, 1H, J = 6.0 Hz); 6.68 (s, 1H)
3g'	1.65 (d, 3H, J = 6.0 Hz); 5.40 (q, J = 6.0 Hz); 6.15 (s, 1H)
3h	1.49 (d, 3H, J = 5.8 Hz); 2.31 (d, 3H, J = 1.8 Hz); 5.34 (q, 1H, J = 5.8 Hz); 5.87 (q, 1H, J = 1.8 Hz)
3h'	1.41 (d, 3H, J = 5.9 Hz); 2.31 (d, 3H, J = 1.4 Hz); 4.80 (q, 1H, J = 5.9 Hz); 6.47 (q, 1H, J = 1.4 Hz)

The regiospecificity[7] of the reaction can be seen in the preparation of compounds **3a, a', 3c, c', 3d, d', 3e, e', 3i, i'**, and **3j, j'** where yields, based on the converted aldehydes, are almost quantitative.

In the case of R^2, $R^4 \neq H$, the reaction is diastereogenic[8]. The ratio of the diastereomers obtained was determined by ^{1}H-N.M.R. analysis; in most cases, both diastereoisomers could be isolated in pure form by column chromatography.

The cyclocondensation appears to be reversible at least in certain cases as can be seen from the fact that treatment of 2-trideuteromethyl-4-(4-chlorophenyl)-6*H*-1,3,5-oxathiazine (**3**, $R^4 = CD_3$) with acetaldehyde in acetic acid containing sulfuric acid leads to the formation of the 2-methyl derivative (**3**, $R^4 = CH_3$)[9].

The mechanism of the cyclocondensation of *N*-(hydroxymethyl)- or *N*-(1-alkoxyalkyl)-thiocarboxamides with aldehydes probably involves a polar 1,4-cycloaddition[10,11] of the ion **5** on aldehydes.



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We do not exclude that a different mechanism may be operative in the reaction of *N*-(1-hydroxy-2,2,2-trichloroethyl)-thiocarboxamides with aldehydes.

The structures of all compounds **3** follow unambiguously from their mass spectra and their I.R.-, ^{1}H-N.M.R.-, and ^{13}C-N.M.R.-spectral data. Significant ^{1}H-N.M.R. data of some representative compounds **3** are given in Table 2.

Melting points were determined with a Kofler hot-stage apparatus and are not corrected. The ^{1}H-N.M.R. spectra of compounds (**3a, 3e, e'-3g, g'**) and **3h, h'** were taken at 60 and 90 MHz, respectively. The spectra of compounds **3a, 3e, e'-3g, g'** were recorded for convenience on the 1.5 Hz/mm scale, the limits of error of the listed coupling constants therefore being ±1 Hz. *N*-(Hydroxymethyl)-4-chlorothiobenzamide[5], *N*-(1-alkoxyalkyl)-thiobenzamides[3], and *N*-(1-hydroxy-2,2,2-trichloroethyl)-thiobenzamides[4] were prepared by previously described procedures.

***N*-(1-Hydroxy-2,2,2-trichloroethyl)-4-chlorothiobenzamide:**
4-Chlorothiobenzamide (21.4 g, 0.125 mol) and chloral (30 ml, 0.3 mol) are dissolved in dry ether (200 ml). After standing at room temperature for 48 h, the reaction mixture is evaporated to dryness. The residue is crystallized from carbon tetrachloride; yield 35.9 g (90%); m.p. 104–106° (from CCl_4).

$C_9H_7Cl_4NOS$	calc.	C 33.88	H 2.21	N 4.39	Cl 44.45
(319.0)	found	33.72	2.20	4.35	44.25

4-(4-Chlorophenyl)-2-methyl-6-phenyl-6*H*-1,3,5-oxathiazine (Diastereoisomers 3g and 3g'); Method A:
Boron trifluoride etherate (d = 1.13; 3.75 ml, 30 mmol) is added, over 5 min, to a stirred mixture of *N*-(α-methoxybenzyl)-4-chlorothiobenzamide (4.35 g, 15 mmol), acetaldehyde (0.66 g, 15 mmol), and chloroform (15 ml) at 0–5°. The mixture is stirred at room temperature for 30 min, then poured into a saturated sodium carbonate solution, and extracted with ether. The solvent is removed in vacuo and the residue (from ^{1}H-N.M.R. analysis: **3g'/3g** = 3/1) chromatographed on silica gel (70–230 mesh) using pentane/ether (96/4) as eluent to give a mixture of compounds **3g** and **3g'**; yield: 3.7 g (81%). This mixture of diastereoisomers is chromatographed on silica gel using pentane/ether (98/2) as eluent. Two fractions are collected.

Fraction I (0.90 g) is crystallized from acetonitrile to give **3g** as analytically pure product; m.p. 94–96°.

$C_{16}H_{14}ClNOS$	calc.	C 63.25	H 4.64	N 4.61	S 10.55
(303.8)	found	63.20	4.61	4.67	10.63

Fraction II (2.8 g) is crystallized from hexane to give analytically pure **3g'**; m.p. 116–117°.

$C_{16}H_{14}ClNOS$	calc.	C 63.25	H 4.69	N 4.61	S 10.55
(303.8)	found	63.29	4.70	4.58	10.65

2,4-Bis[4-chlorophenyl]-6-trichloromethyl-6*H*-1,3,5-oxathiazine (Diastereoisomers 3e and 3e'); Method B:
A mixture of 4-chlorobenzaldehyde (0.46 g, 3.2 mmol) and *N*-(1-hydroxy-2,2,2-trichloroethyl)-4-chloro-thiobenzamide (1 g, 3.2 mmol) is added, with stirring to methanesulfonic acid (10 ml) at room temperature. Stirring is continued at room temperature for 24 h, the mixture then poured into a saturated sodium carbonate solution, and extracted with ether. The solvent is removed in vacuo and the residue (from ^{1}H-N.M.R. analysis: **3e'/3e** = 12/1) chromatographed on silica gel (70–230 mesh) using pentane/ether (90/10) as eluent to give a mixture of compounds **3e** and **3e'**; yield: 1.41 g (92%). This mixture of diastereoisomers is chromatographed on silica gel using pentane/ether (97/3) as eluent. Two fractions are collected.

Fraction I (0.15 g) is a mixture of **3e** and of **3e'**.

Fraction II (1.26 g) is crystallized from acetonitrile to give analytically pure **3e'**; m.p. 119–120°.

$C_{16}H_{10}Cl_5NOS$	calc.	C 43.51	H 2.28	N 3.17	S 7.26
(441.6)	found	43.55	2.34	3.27	7.36

2,4-Bis[4-chlorophenyl]-6*H*-1,3,5-oxathiazine (3a); Method C:
Methanesulfonic acid (d = 1.48; 4 ml, 62 mmol) is added to a stirred mixture of *N*-(hydroxymethyl)-4-chloro-thiobenzamide (2.02 g, 10 mmol), 4-chlorobenzaldehyde (1.41 g, 10 mmol), and liquid sulfur dioxide (~30 ml) at −70°. The mixture is then allowed to warm to −20°, stirred at this temperature for 2 h, and then poured into cold saturated sodium carbonate solution. The resultant mixture is extracted with ether, the extract dried with Na_2SO_4, and the solvent evaporated in vacuo. The residue is chromatographed on silica gel (70–230 mesh) using pentane/ether (95/5) as eluent; yield of **3a**: 2.33 g (71%). Crystallization from acetonitrile affords analytically pure **3a**; m.p. 135°.

$C_{15}H_{11}Cl_2NOS$	calc.	C 55.56	H 3.42	N 4.32	S 9.89
(324.2)	found	55.50	3.46	4.37	9.85

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