4H-1,3,5-Thiadiazines by α-Thioamidoalkylation of Nitriles

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We wish to report that 4H-1,3,5-thiadiazines (**1**) can be easily obtained from three component systems thioamide/aldehyde/nitrile.

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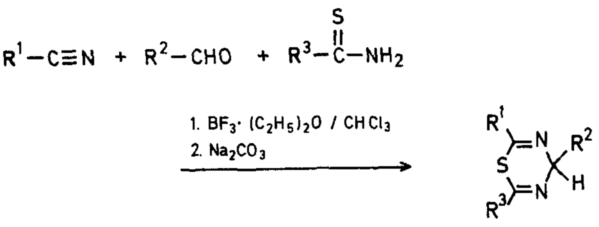
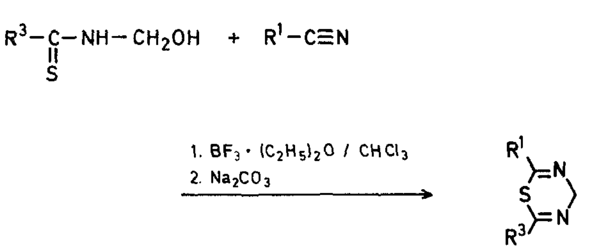
The method[1] consists of adding at room temperature boron trifluoride/ether complex to a solution or a suspension of aldehyde, thioamide, and nitrile in chloroform. Alkaline hydrolysis gives the 4*H*-1,3,5-thiadiazine as the free base **1** (Scheme **A** and Table 1).



1

Scheme **A**

Better yields are obtained using *N*-hydroxymethylthioamides[2], instead of the α-thioamidomethylating agents thioamides plus formaldehyde, in the reaction with nitriles (Scheme **B**).

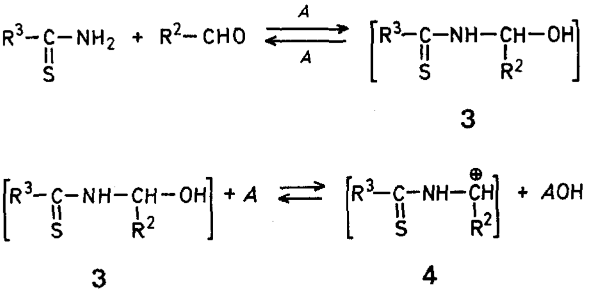


2

The assigned structures for compounds (**1a–j**) follow particularly from the available N.M.R., I.R., and mass[3] spectral data (Table 2) and from base catalysed interconversion of compounds (**1c–h**) into the corresponding imidazoles[4].

Moreover, the presence of seven resonances and of eight resonances in the proton-decoupled ^{13}C-N.M.R.-spectra, (Table 2) respectively of compounds **1b** and **1c**, is consistent with the symmetry of these molecules.

The most likely reaction scheme, based on the literature of α-thioamidoalkylation of olefins[5,6] and of α-amidomethylation of nitriles[7], is a polar 1,4-cycloaddition of thioamidoalkyl ions to the nitriles.



A = electron acceptor

Table 2. ^{1}H- and ^{13}C-N.M.R. and Mass Spectral Data for Products **1a–j**

Product[c]	^{1}H-N.M.R.[a] δ ppm	^{13}C-N.M.R.[a,b] δ ppm	Mass spectra m/e $M^{\oplus}$
1a	5.52 (s, 2H)	—	252
1b	2.06 (d, 3H), 4.57 (q, 1H), J_{H,CH_3} = 6.6 Hz	158.6, 136.1, 131.3, 128.5, 127.5, 77.3, 23.0	266
1c	5.41 (s, 1H)	159.5, 142.1, 136.0, 131.6, 128.6, 128.4, 127.8, 82.8	328
1d	5.43 (s, 1H)	—	342
1e	5.33 (s, 1H)	—	362 (^{35}Cl)
1f	5.38 (s, 1H)	—	356
1g	5.41 (s, 1H)	—	388
1h	5.41 (s, 1H)	—	396 (^{35}Cl)
1i	5.33 (s, 1H)	—	372
1j	5.46 (s, 1H)	—	392 (^{35}Cl)

[a] Solvent: $CDCl_3$; internal standard: TMS.

[b] Proton-decoupled; 22.63 MHz.

[c] In the I.R. spectra of all compounds medium to strong bands were observed at 6.13–6.30 μ, no bands in the N—H, O—H stretching region.

Table 1. Preparation of 4*H*-1,3,5-Thiadiazines (**1**)[a,b]

Product	R^1	R^2	R^3	Yield (%)	m.p.[c]
1a	C_6H_5	H	C_6H_5	24[d,e]	82–83° (Lit.[8]: 80°)
1b	C_6H_5	CH_3	C_6H_5	73[d]	108–109°
1c	C_6H_5	C_6H_5	C_6H_5	63[d]	146–147°
1d	C_6H_5	4-H_3C—C_6H_4	C_6H_5	61[d]	142–143°
1e	C_6H_5	4-Cl—C_6H_4	C_6H_5	65[d]	158–159°
1f	4-H_3C—C_6H_4	C_6H_5	4-H_3C—C_6H_4	61[d]	116–117°
1g	4-H_3CO—C_6H_4	C_6H_5	4-H_3CO—C_6H_4	95[f]	141–142°
1h	4-Cl—C_6H_4	C_6H_5	4-Cl—C_6H_4	75[d]	149–151°
1i	4-H_3C—C_6H_4	C_6H_5	4-H_3CO—C_6H_4	45[f,g]	111–112°
1j	4-Cl—C_6H_4	C_6H_5	4-H_3CO—C_6H_4	41[f,h]	123–125°

[a] The experimental procedure followed for the preparation of 4*H*-1,3,5-thiadiazines **1a–j** is that described in the synthesis of compound **1f**.

[b] Satisfactory analytical data were obtained for all new compounds.

[c] Melting points were determined by the Kofler method and were not corrected. Heptane was used as crystallization solvent.

[d] Yield of the pure analytical product, isolated as described in the experimental part.

[e] A 54% yield was obtained using *N*-hydroxymethylthiobenzamide instead of the α-thioamidomethylating agent-thiobenzamide plus formaldehyde (1,3,5-trioxane).

[f] Yield of the product isolated via chromatography on SiO_2.

[g] Thiadiazines **1f** and **1g** were isolated as by-products respectively in 16% and 18% yield.

[h] Thiadiazines **1g** and **1h** were isolated as by-products in 13% and 19% yield.

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2,6-Bis[4-methylphenyl]-4-phenyl-4*H*-1,3,5-thiadiazine (1f):
To a stirred mixture of 4-methylthiobenzamide (9.1 g, 0.06 mol), 4-methylbenzonitrile (7 g, 0.06 mol), and benzaldehyde (6.4 g, 0.06 mol) in chloroform (30 ml), kept at 0–5°, boron trifluoride/ether (15 ml, d = 1.13, 0.12 mol) was added during 10 min. The resulting solution was kept for 1 h at this temperature and for 16 h at 15°.

The reaction mixture was poured into ice, made alkaline with sodium carbonate saturated solution, and extracted with diethyl ether. The solvent was distilled in vacuum and the solid residue was suspended in diethyl ether and filtered to give **1f**; yield: 12.6 g.

The solvent was distilled in vacuum from the ethereal liquor mother. Chromatography of residue (8.6 g) on SiO_2 (160 g, 70–230 mesh) using petroleum ether (40–60°)/diethyl ether (95:5) as eluent gave **1f**; yield: 2.9 g.

The two crops were brought together and crystallized from *n*-heptane to give **1f**; yield: 13 g (61%) as pure analytical product: m.p. 116–117°.

$C_{23}H_{20}N_2S$	calc.	C 77.49	H 5.66	N 7.86	S 8.99
(356.46)	found	77.52	5.71	7.72	8.77

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