5,6-Dihydro-4*H*-1,3-thiazines from Olefins

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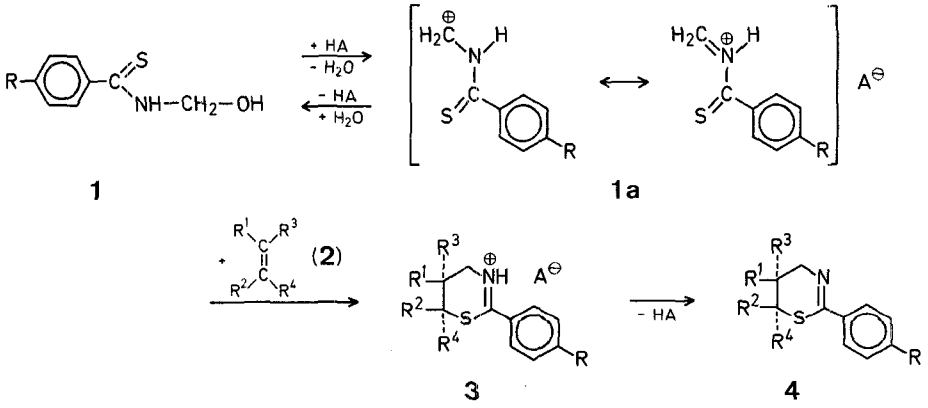
We have recently described the synthesis of 5,6-dihydro-4*H*-1,3-oxazines[1] from olefins and amidomethylating agents. Now we wish to report on a new method of synthesis of 2-aryl-5,6-dihydro-4*H*-1,3-thiazines (**4**)[2].

Compounds **4** are obtained by adding an acid catalyst (hydrogen chloride or sulfuric acid) to a solution containing an N-(hydroxymethyl)-thiobenzamide[3] (**1**) and an olefin (**2**) in acetic acid at room temperature.

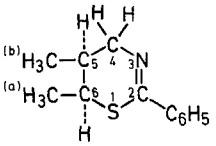


1 **1a** **3** **4**

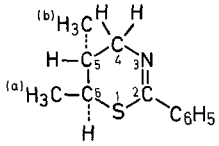
The replacement of N-(hydroxymethyl)-thiobenzamides (**1**) by other thioamidomethylating agents such as thiobenzamides plus formaldehyde (1,3,5-trioxane) leads to a remarkable decrease in the yields of **4**. Likewise, under our experimental conditions the use of N-(hydroxymethyl)-thioacetamide leads to poor preparative results.

Physical properties and yields of some 5,6-dihydro-4*H*-1,3-thiazines (**4**) obtained are listed in Table 2.

The reaction described is analogous to that of N-(hydroxymethyl)-carboxamides[4] with olefins and is to be regarded as a regiospecific[5] *cis* cycloaddition of the thioamidomethyl ion (**1a**) to the olefin (**2**). Evidence is given by the N.M.R. spectra of compounds **4a** and **4b**, obtained from *cis*- and *trans*-butene, respectively.



4a



4b

Table 1. N.M.R. Data of Compounds **4a** and **4b**.

		Chemical shifts δ [ppm]					Coupling constants J [Hz]			
		H_4	H_5	H_6	a	b	$J_{4,5}$	$J_{6,5}$	$J_{a,6}$	$J_{b,5}$
4a	($CDCl_3$)	3.78	1.98	3.38	1.21	0.89	5.2	3.3	7.0	6.9
4b	(C_6D_6)	—	1.2	2.76	1.05	0.69	—	8.4	6.8	6.8

thiobenzamides (**1**) were prepared according to the method of Böhme and Hotzel[3]. The *p*-chloro and *p*-methyl derivatives had not been described before.

4-Chloro-N-(hydroxymethyl)-thiobenzamide (1, R = Cl):
A 35% aqueous solution of formaldehyde (105 ml, $d^{18} = 1.1066$, 1.36 mol) is added to 4-chlorothiobenzamide (15.3 g, 0.0894 mol) suspended in water (1750 ml) at 90°. The solution is then brought to 100° and kept at this temperature for 15 minutes. After cooling, it is extracted with ether. On distillation, the dried ethereal extracts leave 14.5 g of product; m.p. 84–87°; after one recrystallization from ether, m.p. 90–91°.

2-(4-Chlorophenyl)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazine (4e):
100% sulfuric acid (4.4 g, 0.045 mol) is added dropwise to a solution of 4-chloro-N-(hydroxymethyl)-thiobenzamide (9.1 g, 0.045 mol) and styrene (4.7 g, 0.045 mol) in glacial acetic acid (70 g) at ~15°. After the addition is complete, the solution is kept at this temperature for 6 hr and allowed to stand at room temperature overnight. The reaction mixture is then poured onto ice, made alkaline with 40% aqueous sodium hydroxide (keeping the temperature at ~10°), and extracted with ether. The ether extract is washed with 2 *N* hydrochloric acid (2 × 50 ml) at ~10°. The acid aqueous extracts are made alkaline by the addition of 40% aqueous sodium hydroxide at ~10°, and extracted with ether (3 × 160 ml). The ether extracts are evaporated and the residue, which crystallizes, is washed with cold ether; yield: 6.5 g (50%); m.p. 96–97°.

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Table 2. 2-Aryl-5,6-dihydro-4*H*-1,3-thiazines (**4**) from N-(Hydroxymethyl)-thiobenzamides (**1**) and Olefins (**2**)

	R	R^1	R^2	R^3	R^4	Yield %[a]	m.p.[b] or b.p.
a	H	CH_3	CH_3	H	H	31.5[c]	b.p. 110–111°/0.5 torr
b	H	H	CH_3	CH_3	H	20	m.p. 53–54°
c	H	H	H	H	C_6H_5	37.5[d]	m.p. 89–90° (86.5–87.5°[6])
d	H	H	H	H	$-CH=CH_2$	16[c]	b.p. 112°/0.1 torr (Ref.[8], m.p. 86.5–87.5°)
e	Cl	H	H	H	C_6H_5	50	m.p. 96–97°
f	CH_3	H	H	H	C_6H_5	48	m.p. 110–112°

[a] The 5,6-dihydro-4*H*-1,3-thiazines contain the corresponding 5,6-dihydro-4*H*-1,3-oxazines as impurities.
[b] The melting points were determined by the Kofler method.
[c] Yields of products **4a** and **4e** were determined by G.L.C. analysis (peak areas ratio) of the distilled crude product.
[d] A 45% yield was obtained using gaseous hydrochloric acid as catalyst.

The structures of the 5,6-dihydro-4*H*-1,3-thiazines (**4**) were determined by means of N.M.R. and I.R. spectrometry.

A study[7,8] of the three-component system olefins/thioamides/aldehydes is in progress to extent the method described here to other thioamidoalkylating agents and to clarify the reaction mechanism.

The experimental method used in carrying out the reaction between the olefins (**2**) and the N-(hydroxymethyl)-thiobenzamides (**1**) (Table 2) is exemplified by the below described preparation of 2-(4-chlorophenyl)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazine (**4e**, R = Cl, $R^1 = R^2 = R^3 = H$, $R^4 = C_6H_5$). The N-(hydroxymethyl)-

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[1] C. Giordano, G. Ribaldone, G. Borsotti, Synthesis **1971**, 92.
[2] C. Giordano, Italian Patent Appl. 22735 A/71.
[3] H. Böhme, H.H. Hotzel, Arch. Pharm. **300**, 241 (1967).
[4] R.R. Schmidt, Chem. Ber. **103**, 3242 (1970), and references cited therein.
[5] A. Hassner, J. Org. Chem. **33**, 2684 (1968).
[6] P.A.S. Smith, J.M. Sullivan, J. Org. Chem. **26**, 1132 (1961).
[7] C. Giordano, Italian Patent Appl. 27801 A/71.
[8] C. Giordano, L. Abis, work in progress.