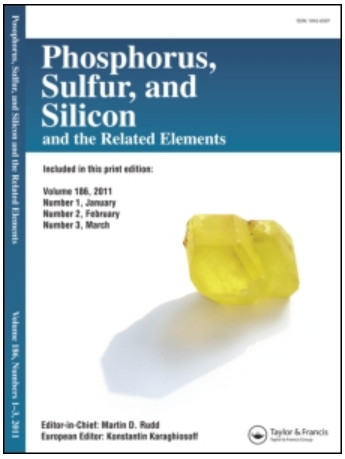

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SYNTHESIS AND REACTIONS OF HALO DERIVATIVES OF 4-ISOPROPYL-2H-1,4-THIAZIN-3-ONE

Ryhi Masuda[a]; Masaru Hojo[a]; Tadaaki Ichi[a]; Fujio Adachi[a]; Kenji Yoshinaga[a]
[a] Department of Industrial Chemistry, Faculty of Engineering, Kobe University, Rokkodai, Kobe, Japan

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SYNTHESIS AND REACTIONS OF HALO DERIVATIVES OF 4-ISOPROPYL-2H-1,4-THIAZIN-3-ONE

RYŌICHI MASUDA, MASARU HOJO,* TADAAKI ICHI, FUJIO ADACHI and KENJI YOSHINAGA

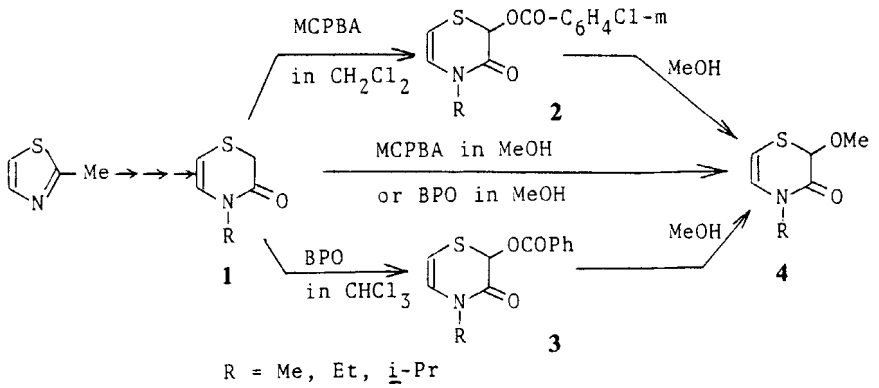
Department of Industrial Chemistry, Faculty of Engineering, Kobe University, Rokkodai, Kobe 657, Japan

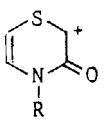
(*Received December 19, 1982*)

Reaction of 4-isopropyl-2H-1,4-thiazin-3-one **1** (R = *i*-Pr) with *N*-chloro- and *N*-bromosuccinimide occurred exclusively at the 6-position to give 6-chloro and 6-bromo derivatives of **1** (R = *i*-Pr), respectively, in high yield, in sharp contrast to the 2-aroyloxylation by benzoyl peroxide or *m*-chloroperbenzoic acid reported earlier.[2] Reaction of **1** (R = *i*-Pr) with methanesulfonyl chloride in the presence of aluminum chloride afforded an addition compound, 4-isopropyl-5,6-dichloro-1,4-tetrahydrothiazin-3-one. The 2-chloro derivative **6** of **1** (R = *i*-Pr) was successfully prepared by hydrolysis of the 2-*m*-chlorobenzoyloxy derivative of **1** (R = *i*-Pr) followed by treatment with thionyl chloride. Derivative **6** reacted readily under mild conditions with water, alcohols, thiols, ammonia and amines to give various 2-substituted compounds of **1** (R = *i*-Pr). With phenol as a nucleophile, **1** (R = *i*-Pr) reacted exclusively at the para position. Reaction at carbon atoms also occurred with *N*,*N*-dimethylaniline and 2,6-xylidine.

INTRODUCTION

Recently we reported[1] a new convenient synthetic method for 4-alkyl-2H-1,4-thiazin-3-ones (**1**) from 2-methylthiazole involving a novel skeletal rearrangement. On treatment of this compound (**1**) with *m*-chloroperbenzoic acid in dichloromethane at room temperature, the 2-(*m*-chlorobenzoyloxy)-derivative (**2**) of **1** was obtained as sole product in an almost quantitative yield.[2] This reaction is strongly accelerated by light; under irradiation with a UV lamp, this reaction is complete within 30 min. Likewise, benzoyl peroxide reacted with **1** to give the 2-benzoyloxy derivative (**3**) in high yields.[2] Interestingly, when this aroyloxylation was carried out in methanol as a solvent, 2-methoxy compounds (**4**) were cleanly produced.[3] This finding prompted





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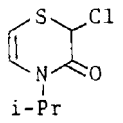


6

us to investigate the reactions of these 2-aroyloxy derivatives (**2** and **3**) with some nucleophiles and it was found that these reactions proceeded with exclusive *alkyl-oxygen bond fission* of the benzoates (**2** and **3**).[4]

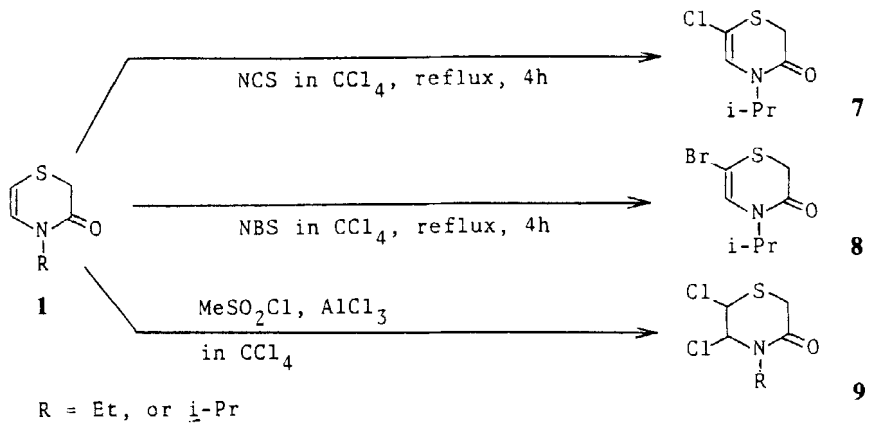
The present work was initiated to synthesize the 2-chloro derivative (**6**) of **1**. The 2-chloro derivative **6** might react with different nucleophiles including carbon nucleophiles to give various kinds of products. In this paper are described the synthesis and reactions of 2-chloro-4-isopropyl-2H-1,4-thiazin-3-one (**6**), together with the synthesis of 6-chloro and 6-bromo derivatives of **1** and some related data.

RESULTS AND DISCUSSION

6-Halo-4-Isopropyl-2H-1,4-Thiazin-3-Ones

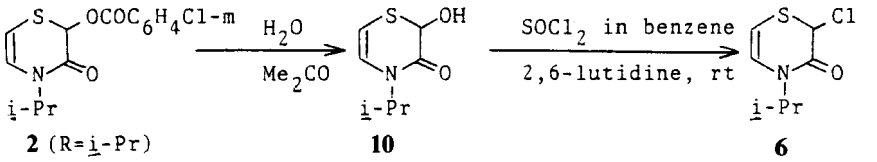
As is the case in the highly selective 2-aroyloxylation of **1**, free-radical chlorination of **1** (R = *i*-Pr) was expected to give the 2-chloro derivative (**6**). Actually, however, when *N*-chlorosuccinimide was used as a chlorinating reagent, the 6-chloro derivative **7** was obtained as a sole product almost quantitatively. Likewise, the 6-bromo compound **8** was successfully prepared by bromination of **1** (R = *i*-Pr) with *N*-bromosuccinimide in a quantitative yield. The two halo derivatives proved to be practically pure by ^{1}H-nmr but could not be purified by distillation **in vacuo**. However, these compounds, **7** and **8**, could be converted to the crystalline 2-*m*-chlorobenzoyloxy-6-halo derivatives by treatment with *m*-chloroperbenzoic acid.

Attempted chlorination of **1** (R = Et, *i*-Pr) with methanesulfonyl chloride in the presence of aluminum chloride resulted in the formation of addition products (**9**, R = Et, *i*-Pr) in 86–91% yield. Interestingly, treatment of these chlorides with *m*-chlorobenzoic acid gave the corresponding sulfoxides, in sharp contrast to the case of **1**, **7** and **8** where *m*-chlorobenzoyloxylation at the 2-position occurred exclusively.



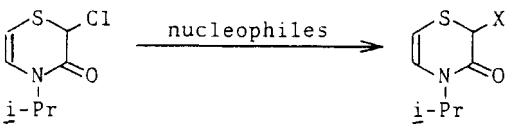
Synthesis of 2-Chloro-4-Isopropyl-2H-1,4-Thiazin-3-One (6)

The 2-*m*-chlorobenzoyloxy derivative (**2**, R = *i*-Pr) was hydrolysed by dissolving in acetone containing a small amount of water to give the 2-hydroxy compound (**10**). The 2-hydroxy derivative was then converted into the 2-chloroderivative **6** in quantitative yields by reaction with thionyl chloride in benzene in the presence of 2,6-lutidine. As anticipated, the chloride **6** is not stable and gradually decomposed on storage at room temperature. Therefore, the chloride **6** was prepared just before use.

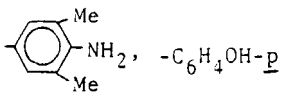


Reactions of 2-Chloro-4-Isopropyl-2H-1,4-Thiazin-3-One (6) with Nucleophiles

The chloro compound (**6**) was readily converted back into the 2-alcohol (**10**) by treatment with a small amount of water in acetone as a solvent at room temperature. This alcohol is soluble in water and is converted to the benzoate (**3**, R = *i*-Pr). Reactions of **6** with methanol, ethanol and *i*-propyl alcohol under solvolytic conditions proceeded cleanly and very rapidly within 30 min at room temperature to give 2-OMe, 2-OEt and 2-OPr-*i* derivatives, respectively, all in high yields. Thiols also reacted with **6** to afford almost quantitative yields of the corresponding sulfides. The 2-NH_2 derivative was obtained in 92% yield by dissolving **6** in acetone containing a small amount of an aqueous solution of ammonia at room temperature. The 2-NH_2 compound is also soluble in water and gave an *N*-*p*-nitrobenzoyl derivative. Similarly, the 2-isopropylamino compound was also prepared.



X = -OH, -OMe, -OEt, -OPr^{i}, -SMe, -$SC_6H_4NO_2$-p, -NH_2, -$NHPr^{i}$, -$C_6H_4NMe_2$-p,

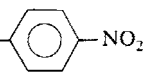
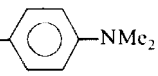
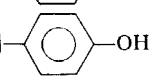
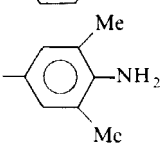
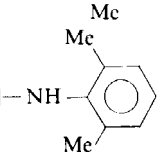


-C_6H_4OH-p

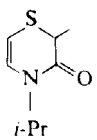
In order to test for possible high reactivity of the 2-chloro compound **6**, phenol was chosen as an ambident nucleophile. As expected, reaction occurred exclusively at the para carbon in preference to the oxygen. Alkylation at carbon also occurred with dimethylaniline, affording the 2-*p*-dimethylaminophenyl derivative. In the case of 2,6-xylidine as a nucleophile, some *N*-alkylated compound was produced, together with the 4-substituted 2,6-xylidine as a main product. The results are summarized in Table I.

TABLE I

Reactions of **6** with nucleophilic reagents[a]

Nucleophile	Time (h)	Solvent	Product[b] [R]—X	Yield (%)	mp (°C), (bp/torr)
H_2O	10 min	Me_2CO	[R]—OH	70.0	oil
MeOH	0.5	MeOH	[R]—OMe	86.2	(160/10)
EtOH	0.5	EtOH	[R]—OEt	84.8	(215/5)
i-PrOH	0.5	*i*-PrOH	[R]—OPr-*i*	93.0	(207/13)
MeSH	1	MeOH-Me_2CO	[R]—SMe	93.6	38
p-$O_2NC_6H_4SH$	3	CH_2Cl_2	[R]—S—  —NO_2	93.2	105
NH_3aq	5 min	Me_2CO	[R]—NH_2	92.1	oil
i-$PrNH_2$	5	Me_2CO	[R]—NHPr-*i*	83.9	60
$PhNMe_2$[c]	24	CH_2Cl_2	[R]—  —NMe_2	36.2	82
PhOH	2d	CH_2Cl_2	[R]—  —OH	68.9	94
2,6-Me_2-1-NH_2—C_6H_3	24	CH_2Cl_2	[R]—  —NH_2	58.3	125
			[R]—NH— 	19.8	oil

[a]At room temperature.

[b][R] denotes 

[c]Added SiO_2 (200 wt%).

EXPERIMENTAL

All melting points are uncorrected. Data for microanalysis of all materials together with their spectroscopic data are presented in Table II.

Preparation of 6-Halo derivatives of 4-Isopropyl-2H-1,4-thiazin-3-ones

6-Chloro-4-isopropyl-2H-1,4-thiazin-3-one **7**. To a solution of **1** (R = *i*-Pr, 258 mg, 1.63 mmol) in carbon tetrachloride was added 240 mg (1.79 mmol) of *N*-chlorosuccinimide and the mixture was refluxed for 18 hr. After evaporation of the solvent **in vacuo**, the mixture was extracted with *n*-hexane and the solvent removed to give 327 mg (yield 100%) of the practically pure (by ^{1}H-nmr, Table II) product **7** as a yellow oil. This compound gradually decomposed on standing at room temperature and was confirmed as the crystalline 6-chloro-2-*m*-chlorobenzoate. A mixture of **7** (327 mg, 1.71 mmol), *m*-chloroperbenzoic acid (295 mg, 1.71 mmol) and dichloromethane (10 ml) was allowed to stand for 3 days at room temperature. After evaporation of the solvent, the residue was chromatographed over silica gel. There was obtained 149 mg (yield 25%) of 2-*m*-chlorobenzoyloxy-6-chloro-4-isopropyl-2H-1,4-thiazin-3-one from a fraction eluted by *n*-hexane–benzene (3 : 7), together with recovery of 183 mg (56%) of **7** from benzene–ethyl acetate (9 : 1). The pure 6-chloro-2-*m*-chlorobenzoate melted at 101° (from *n*-hexane-chloroform).

TABLE II

Characterization of compounds

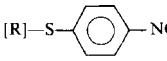
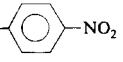
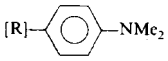
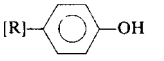
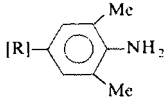
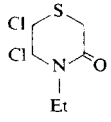
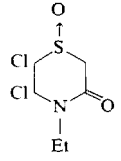
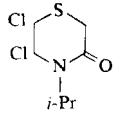
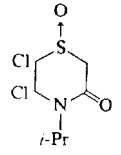
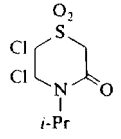
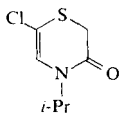
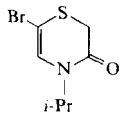
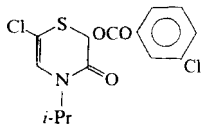
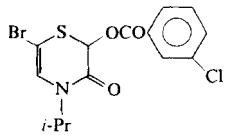
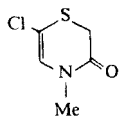
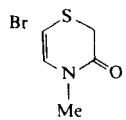
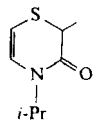
Compound[a]	mp (°) (bp/torr)	^{1}H-nmr (in $CDCl_3$, δ in ppm)	ir (ν_{CO} in cm^{-1})	Formula	Calcd. (%) H C N S Cl Found (%) H C N S Cl
[R]—OH	oil	6.36 (d, 1 H, J = 7.8 Hz), 5.69 (d, 1 H, J = 7.8 Hz), 5.15 (s, 1 H), 5.07 (s, 1 H), 4.85 (h, 1 H, J = 7.2 Hz), 1.25 (d, 6 H, J = 6.0 Hz)	1650 (ν_{OH} 3300)		
[R]—OMe	(160/10)	6.42 (d, 1 H, J = 7.8 Hz), 5.49 (d-d, J = 7.8 Hz, 2.4 Hz), 4.90 (h, 1 H, J = 6.0 Hz), 4.83 (d, 1 H, J = 2.4 Hz), 3.40 (s, 3 H), 1.26 (d, 3 H, J = 6.0 Hz), 1.21 (d, 3 H, J = 6.0 Hz)	1663	$C_8H_{13}SNO_2$	6.99 51.31 7.48 17.12 7.13 51.13 7.49 17.19
[R]—OEt	(215/5)	6.46 (d, 1 H, J = 7.8 Hz), 5.49 (d-d, 1 H, J = 7.8 Hz, J = 3.0 Hz), 4.90 (d, 1 H, J = 3.0 Hz), 4.90 (h, 1 H, J = 6.0 Hz), 3.60 (d-q, 2 H, J = 9.6 Hz), 1.16 (m, 9 H)	1657	$C_9H_{15}SNO_2$	7.51 53.70 6.96 15.93 7.66 53.98 7.01 15.93
[R]—OPr-*i*	(207/13)	6.40 (d, 1 H, J = 7.8 Hz), 5.47 (d-d, 1 H, J = 7.8 Hz, 2.4 Hz), 4.96 (d, 1 H, J = 2.4 Hz), 4.87 (h, 1 H, J = 7.2 Hz), 4.00 (h, 1H, J = 7.2 Hz), 1.17 (m, 12H)	1657	$C_{10}H_{17}SNO_2$	7.96 55.78 6.51 14.89 8.11 55.72 6.54 14.77
[R]—SMe	38	6.41 (d, 1 H, J = 7.8 Hz), 5.54 (d-d, 1 H, J = 7.8 Hz, 1.8 Hz), 4.91 (h, 1 H, J = 7.2 Hz), 4.38 (d, 1 H, J = 1.8 Hz), 2.22 (s, 3 H), 1.23 (d, 6 H, J = 7.2 Hz)	1635	$C_8H_{13}NS_2O$	6.44 47.26 6.89 31.54 6.62 47.54 6.91 31.37
[R]—S—  —NO_2	105	7.85 (q, 4 H), 6.47 (d, 1 H, J = 7.2 Hz), 5.59 (d-d, 1 H, J = 7.2 Hz, 1.8 Hz), 4.88 (d, 1 H, J = 1.8 Hz), 4.70 (h, 1 H, J = 7.2 Hz), 1.20 (d, 6 H, J = 7.2 Hz)	1648 (ν_{NO_2}1511,1340)	$C_{13}H_{14}N_2S_2O_3$	4.55 50.30 9.03 20.66 4.33 50.35 8.83 20.54
[R]—NH_2	oil	6.32 (d, 1 H, J = 7.2 Hz), 5.19 (d, 1 H, J = 7.2 Hz), 4.81 (h, 1 H, J = 6.6 Hz), 4.46 (s, 2 H), 2.80-2.00 (br, 2 H), 1.20 (d, 6 H, J = 6.6 Hz)	1650 (ν_{NH_2}3350, 3280,1605)	—	— — — —
[R]—NHCO—  —NO_2	124	8.34 (d, 2 H, J = 8.4 Hz), 8.04 (d, J = 8.4 Hz), 7.85 (br, 1 H), 6.42 (d, 1 H, J = 7.8 Hz), 5.55 (d, 1 H, J = 7.2 Hz), 4.84 (h, 1 H, J = 6.6 Hz), 1.29 (d, 3 H, J = 6.6 Hz), 1.25 (d, 3 H, J = 6.6 Hz)	1660, 1640 (ν_{NH}3290, ν_{NO_2} 1523,1350)	$C_{14}H_{15}N_3SO_4$	4.70 52.33 13.08 9.98 4.93 52.13 13.11 10.14
[R]—NHPr-*i*	60	6.37 (d, 1 H, J = 7.2 Hz), 5.58 (d-d, 1 H, J = 7.2 Hz, 1.8 Hz), 4.84 (sep, 1 H, J = 7.2 Hz), 4.43 (d, 1 H, J = 1.8 Hz), 3.10 (sep, 1 H, J = 7.2 Hz), 2.08 (s, 1 H), 1.22 (d, 6 H, J = 7.2 Hz), 1.09 (d, 6 H, J = 7.2 Hz)	1650	$C_{10}H_{18}N_2SO$	8.47 56.04 13.07 14.96 8.50 56.29 13.05 14.89
[R]—  —NMe_2	82	7.20 (d, 2 H, J = 8.4 Hz), 6.65 (d, 2 H, J = 8.4 Hz), 6.34 (d, 1 H, J = 7.2 Hz), 5.62 (d-d, 1 H, J = 7.2 Hz, 1.2 Hz), 4.98 (sep, 1 H, J = 7.2 Hz), 4.45 (d, 1 H, J = 1.2 Hz), 2.90 (s, 6 H), 1.22 (d, 6 H, J = 7.2 Hz)	1670	$C_{15}H_{20}N_2SO$	7.29 65.18 11.60 10.13 7.22 64.90 11.64 10.03
[R]—  —OH	94–95	7.04 (d, 2 H, J = 9.0 Hz), 6.57 (d, 2 H, J = 9.0 Hz), 6.23 (d, 1 H, J = 7.2 Hz), 5.61 (d-d, 1 H, J = 7.2 Hz, 1.2 Hz), 4.91 (h, 1 H, J = 6.6 Hz), 4.42 (d, 1 H, J = 1.2 Hz), 1.21 (d, 6 H, J = 6.6 Hz), 6.1 (br, 1 H, disappears with D_2O)	1630 (ν_{OH}3200)	$C_{13}H_{15}NSO_2$	6.06 62.62 5.62 12.86 6.17 62.67 5.56 12.56

TABLE II (*Continued*)

Compound[a]	mp (°) (bp/torr)	^{1}H-nmr (in $CDCl_3$, δ in ppm)	ir (ν_{CO} in cm^{-1})	Formula	Calcd. (%) H Found (%) H	C C	N N	S S	Cl Cl
	125	6.86 (s, 2 H), 6.30 (d, 1 H, J = 7.2 Hz), 5.59 (d-d, 1 H, J = 7.2 Hz, 1.2 Hz), 4.98 (h, 1 H, J = 7.2 Hz), 4.36 (d, 1 H, J = 1.2 Hz), 3.25 (s, 2 H), 2.11 (s, 6 H), 1.20 (d, 6H, J = 7.2 Hz)	1658 (ν_{NH_2}3448, 3373)	$C_{15}H_{20}N_2SO$	7.29 7.23	65.18 64.89	10.13 9.90	11.60 11.56	
[R]—Cl	oil	6.54 (d, 1 H, J = 7.2 Hz), 5.56 (d-d, 1 H, J = 7.2 Hz, 2.4 Hz), 5.50 (s, 1 H), 4.84 (h, 1 H, J = 7.2 Hz), 1.26 (d, 3 H, J = 7.2 Hz), 1.20 (d, 3 H, J = 7.2 Hz)	—	—	—	—	—	—	
	oil	6.11 (d, 1 H, J = 2.4 Hz), 5.05 (t, 1 H, J = 2.4 Hz), 3.62 (q-AB, 2 H, J = 15.0 Hz), 4.00-3.05 (m, 2 H), 2.22 (t, 3 H, J = 7.2 Hz)	1680	—	—	—	—	—	
	134–135 (dec)	6.08 (d, 1 H, J = 4.4 Hz), 4.73 (d, 1 H, J = 4.4 Hz), 3.71 (q-AB, 2 H, J = 18.0 Hz), 4.05-2.13 (m, 2 H), 1.24 (t, 3 H, J = 7.2 Hz)	1703 (ν_{SO}1032)	$C_6H_9NSCl_2O_2$	3.94 3.94	31.32 31.36	6.09 5.89	13.93 13.85	30.81 30.65
	108	6.06 (d, 1 H, J = 1.8 Hz), 5.02 (t, 1 H, J = 1.8 Hz), 4.22 (h, 1 H, J = 7.2 Hz), 3.65 (q-AB, 2 H, J = 14.4 Hz), 1.34 (d-d, 6 H, J = 7.2 Hz)	1664	—	—	—	—	—	—
	113	6.16 (d, 1 H, J = 2.4 Hz), 4.83 (d, 1 H, J = 2.4 Hz), 4.36 (h, 1 H, J = 7.2 Hz), 3.74 (q-AB, 2 H, J = 18.0 Hz), 1.34 (d-d, 6 H, J = 7.2 Hz)	1687 (ν_{SO} 1047)	$C_7H_{11}NSCl_2O_2$	4.54 4.68	34.44 34.52	5.74 5.76	13.13 13.15	29.04 28.76
	124	6.38 (d, 1 H, J = 1.0 Hz), 4.97 (s, 1 H), 4.32 (h, 1 H, J = 6.6 Hz), 3.83 (q-AB, 2 H, J = 16.2 Hz), 1.49 (d-d, 6 H, J = 6.6 Hz)	1695 (ν_{SO_2}1320, 1137)	$C_7H_{11}NSCl_2O_3$	4.26 4.09	32.32 32.26	5.39 5.65	12.32 12.59	27.26 27.08

	oil	6.51 (s, 1 H), 4.91 (h, 1 H, J = 7.2 Hz), 3.45 (s, 2 H), 1.25 (d, 6 H, J = 7.2 Hz)	—	—	—	—	—	—	—	
	oil	6.59 (s, 1 H), 4.87 (h, 1 H, J = 7.2 Hz), 3.41 (s, 2 H), 1.25 (d, 6 H, J = 7.2 Hz)	1660	—	—	—	—	—	—	
	101	7.96-7.16 (m, 4 H), 6.65 (s, 1 H), 6.37 (s, 1 H), 4.91 (h, 1 H, J = 7.2 Hz), 1.31 (d-d, 6 H, J = 7.2 Hz)	1676 (ν_{COO}1737)	$C_{13}H_{13}NSCl_2O_3$	3.78 3.78	48.57 48.67	4.05 3.95	9.26 9.40	20.48 20.41	
	114–114.5	8.01-7.22 (m, 4 H), 6.80 (s, 1 H), 6.38 (s, 1 H), 4.92 (h, 1 H, J = 7.2 Hz), 1.29 (d-d, 6 H, J = 7.2 Hz)	1675 (ν_{COO}1736)	$C_{13}H_{13}NSClBrO$[b]	3.35 3.35	43.04 43.20	3.59 3.42	8.21 8.46	9.07 9.03	
	oil	6.44 (s, 1 H), 3.46 (s, 2 H), 3.13 (s, 3 H)	1660	—	—	—	—	—	—	
	oil	6.55 (s, 1 H), 3.43 (s, 2 H), 3.11 (s, 3 H)	1661	—	—	—	—	—	—	

[a] [R] denotes 

[b] Br: Calcd. 20.45, Found 20.35.

6-Bromo-4-isopropyl-2H-1,4-thiazin-3-one **8**. To a solution of **1** (497 mg, 316 mmol) in carbon tetrachloride (25 ml) was added *N*-bromosuccinimide (622 mg, 3.49 mmol) and the mixture was refluxed for one day. After work-up as described above, 747 mg (100%) of practically pure (by ^{1}H-nmr) product **8** was obtained as an oil which also decomposed gradually at room temperature. This product (1.22 g, 5.16 mmol) was allowed to react with *m*-chloroperbenzoic acid (890 mg, 5.16 mmol) in dichloromethane (25 ml) for 3 days at room temperature. The mixture was washed thoroughly with an aqueous solution of sodium carbonate and the solvent was removed to give a brown residue, which after column chromatography afforded 1.464 g (yield 73%) of 2-*m*-chlorobenzoyloxy-6-bromo-4-isopropyl-2H-1,4-thiazin-3-one (mp. 114.5°, from *n*-hexane–benzene) and 209 mg of recovered material **7**.

5,6-Dichloro-4-alkyltetrahydro-1,4-thiazin-3-ones **9**. To a mixture of **1** (R = *i*-Pr, 816 mg, 5.19 mmol), aluminum chloride (2.03 g, 15.25 mmol) and carbon tetrachloride (15 ml) was added 2.04 g (17.79 mmol) of methanesulfonyl chloride and the mixture was refluxed for 3 h. After usual work-up there was obtained 1.23 g (yield 100%) of 5,6-dichloro-4-isopropyltetrahydro-1,4-thiazin-3-one (**9**) as pale yellow crystals, which melted sharply at 108° (from *n*-hexane). This compound is not stable enough and repeated recrystallization for elemental analysis caused partial decomposition. Therefore **9** was converted into the corresponding sulfoxide and sulfone, which were entirely stable.

Compound **9** (356.8 mg, 1.56 mmol) was dissolved in dichloromethane (10 ml) and *m*-chloroperbenzoic acid (269.9 mg, 1.56 mmol) was added to this solution. The whole mixture was allowed to stand for 3 days at room temperature, giving 333.3 mg (yield 87.3%) of the sulfoxide; mp 113° (from *n*-hexane–chloroform). A mixture of this sulfoxide (366.4 mg, 1.50 mmol), *m*-chloroperbenzoic acid (323.7 mg, 1.50 mmol) and dichloromethane (10 ml) gave, after 10 days at room temperature, 349 mg of solid materials. Column chromatography of this product on silica gel afforded 241.9 mg (yield 89%) of the sulfone, which was eluted by benzene–ethyl acetate (8 : 2); mp. 124° (from chloroform).

In a similar manner 5,6-dichloro-4-ethyltetrahydro-1,4-thiazin-3-one was obtained in 94% yield as an oily material. This compound was oxidized to the crystalline sulfoxide (yield 49%, from chloroform), which melted at 134–135° with decomposition.

Preparation of 2-chloro-4-isopropyl-2H-1,4-thiazin-3-one (**6**)

2-Hydroxy-4-isopropyl-2H-1,4-thiazin-3-one **10**. To a solution of 2-*m*-chlorobenzoyloxy derivative (532.4 mg, 1.71 mmol) in acetone (20 ml) was added 7 ml of water. After stirring for 1 day at room temperature, the solvent was removed **in vacuo**, dichloromethane was added to the residue and the resulting solution was extracted with a small amount of an aqueous solution of sodium carbonate. Evaporation of the solvent gave 183.3 mg (yield 62%) of 2-hydroxy compound **10** as a yellow oil, which is soluble in water. This alcohol **10** was identified by reconverting into the benzoate **3** (R = *i*-Pr); benzoylation with the use of benzoyl chloride and pyridine in benzene as a solvent cleanly gave **3** (R = *i*-Pr).

2-Chloro-4-isopropyl-2H-1,4-thiazin-3-one **6**. To a mixture of alcohol **10** (322.5 mg, 1.88 mmol) and 2,6-lutidine (229.1 mg, 2.07 mmol) in benzene (10 ml) was added dropwise a solution of thionyl chloride (273.3 mg, 2.29 mmol) in benzene (10 ml). After stirring for 5 h at room temperature, 10 ml of *n*-hexane was added to the mixture, which quantitatively precipitated the hydrochloride of 2,6-lutidine. Filtration and evaporation of the filtrate **in vacuo** gave quantitative yields (384 mg) of **6** as a light brown oil. The chloro compound is fairly stable in benzene and carbon tetrachloride, but decomposes spontaneously to resinous materials on removal of the solvents or in contact with silica gel. Therefore, this compound was prepared just before use.

Reactions of 2-Chloro-4-isopropyl-2H-1,4-thiazin-3-one **6** *with nucleophiles.* 2-Chloro compound **6** prepared above was used for subsequent reactions without further purification.

Reaction with water and alcohols. To a solution of **6** prepared from 210 mg (1.226 mmol) of alcohol **10** in acetone was added 7 ml of water and the mixture was stirred for 10 min at room temperature. Evaporation of acetone, dissolution in dichloromethane, washing with an aqueous solution of sodium carbonate and removal of the solvent **in vacuo** gave 147 mg (yield 70%) of alcohol **10**.

2-Chloro-compound **6** (from 184.5 mg, 1.077 mmol of 2-alcohol **10**) was dissolved in 10 ml of methanol and stirred for 30 min at room temperature, which after the usual work up, gave 175 mg (yield 86%) of liquid 2-methoxy derivative; bp. 160°/10 torr. Likewise, reaction of **9** with ethanol and isopropyl alcohol gave 2-ethoxy (yield 85%, bp. 215°/5 torr) and 2-isopropoxy (yield 93%, bp. 207°/13 torr) derivatives, respectively.

Reaction with thiols. 2-Chloro compound **6** (from 213.1 mg, 1.244 mmol of 2-alcohol **10**) was dissolved in 10 ml of acetone, and 5 ml of 30% methanolic solution of methanethiol was added to the above solution.

Stirring for 1 h at room temperature and work-up as usual afforded 237.6 mg (yield 94%) of 2-methylthio compound, mp. 38° (from *n*-hexane–chloroform).

To a solution of 2-chloro compound **6** (from 770.5 mg, 4.499 mmol of 2-alcohol **10**) in dichloromethane (30 ml) was added *p*-nitrothiophenol (2.029 g, 13.08 mmol) and the mixture was stirred at room temperature for 2 h to give pale yellow crystals. On column chromatography (silica gel) of this material, the 2-*p*-nitrophenylthio derivative was eluted by benzene. Recrystallization from benzene–*n*-hexane afforded pure crystals (1.002 g, yield 93%), which melted sharply at 105.5°.

Reaction with ammonia and amines. To a solution of **6** (from 223.0 mg, 1.302 mmol of 2-alcohol **10**) in acetone (5 ml) was added 5 ml of an aqueous solution (28%) of ammonia and stirred for 5 min at room temperature, giving 208.1 mg (yield 92%) of 2-amino derivative as an oily material which proved practically pure by ^{1}H-nmr. This material (185.0 mg, 1.074 mmol) was dissolved in dichloromethane (10 ml) and allowed to react with *p*-nitrobenzoyl chloride (219.5 mg, 1.183 mmol) in the presence of 2,6-lutidine (130.3 mg, 1.213 mmol) for 5 h at room temperature. The mixture was then washed successively with dilute hydrochloric acid, water, aqueous sodium carbonate and finally with water. Evaporation of the solvent gave 379.4 mg (yield 100%) of 2-*p*-nitrobenzoylamino derivative; mp. 124° (from *n*-hexane–carbon tetrachloride).

Compound **6** (from 211.5 mg, 1.235 mmol of 2-alcohol **10**) was treated with a solution of isopropylamine (5 ml) in acetone (10 ml) for 5 min at room temperature to give 222.0 mg (yield 84%) of 2-isopropylamino derivative as orange crystals; mp. 44° (from *n*-hexane–carbon tetrachloride).

Compound **6** (from 267.5 mg, 1.562 mmol of 2-alcohol **10**) was dissolved in 10 ml of dichloromethane. Into this stirred solution was introduced 500 mg of silica gel (Wako-gel C-300, dried for 3 h at 160° under 10 torr) and then 383.2 mg (3.162 mmol) of dimethylaniline. After stirring for 1 day at room temperature, the silica gel was filtered and the solvent was removed to give 154.7 mg of oil, which was chromatographed on silica gel. The 2-*p*-*N*,*N*-dimethylaminophenyl derivative was eluted by benzene-ethyl acetate (4 : 1), 139.3 mg (yield 36%); mp. 82°.

To a solution of compound **6** (from 269.5 mg, 1.573 mmol of 2-alcohol **10**) in dichloromethane (10 ml) was added 2,6-xylidine (395.0 mg, 3.260 mmol) and the mixture was allowed to stand for 1 day to afford 696.0 mg of brown crystalline material, which was chromatographed on silica gel. A fraction eluted by benzene–ethyl acetate (9 : 1) gave 86.0 mg (yield 20%) of 2-(2,6-dimethylanilino) derivative. The 2-(3,5-dimethyl-4-aminophenyl) derivative was eluted by benzene–ethyl acetate (8 : 2) and also by methanol as the hydrochloride. The two crops were combined, dissolved in dichloromethane, washed with aqueous sodium carbonate and the solvent was removed to give 175.3 mg (yield 58.3%) of practically pure compound; mp. 125° (from *n*-hexane–carbon tetrachloride).

Reaction with phenol. To a solution of compound **6** (from 322.5 mg, 1.883 mmol of 2-alcohol **10**) in dichloromethane (5 ml) was added 354.4 mg (3.766 mmol) of phenol. Standing for 2 days at room temperature and evaporation of the solvent gave 348.3 mg of colorless crystals. Purification by column chromatography on silica gel with the use of benzene–ethyl acetate (8 : 2) as an eluent afforded 262.3 mg (yield 68%) of 2-(*p*-hydroxyphenyl) derivative; mp. 94° (from benzene–carbon tetrachloride).

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