A Novel Synthesis of 4*H*-1,3-Thiazin-4-one Derivatives

Masataka YOKOYAMA

Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho, Chiba

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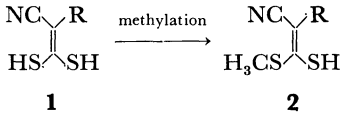
4*H*-2,5,6-Substituted-2,3-dihydro-1,3-thiazin-4-ones were synthesized by the condensation reaction of β-alkylthio-β-mercapto-α-cyanoacrylamide with a variety of ketones and aldehydes in an acidic medium.

The monomethyl ether of enedithiols **1** proved to display different nature according to the R groups (Scheme 1). When R was carbamoyl, the resulting β-methylthio-β-mercapto-α-cyanoacrylamide (**2d**$_1$) was stable colorless needles. When R was alkoxycarbonyl, methyl β-methylthio-β-mercapto-α-cyanoacrylate (**2b**) and ethyl β-methylthio-β-mercapto-α-cyanoacrylate (**2c**) which were obtained as colorless needles, upon heating at 35—40°C, easily changed into stable yellow materials ($C_{12}H_{14}N_2S_5O_4$ for **2b** and $C_{14}H_{18}N_2S_5O_4$ for **2c**). The yellow materials were not examined in the present work. When R was cyano, a dialkyl enedithiol was obtained instead of **2a**. The ease of the complete methylation of **2a** may be due mainly to the less steric hindrance of cyano as the R group.

In view of the NMR and IR spectra of **2d**$_1$, the structure of **2d**$_1$ is probably "zwitterion"; **2d**$_1$ may be more stable than **2b** and **2c** because of this zwitterion structure.

Using the nucleophilic character of the mercapto group of β-alkylthio-β-mercapto-α-cyanoacrylamide (**2d**), the present investigation was directed to exploring the reaction of **2d** with ketones and aldehydes (**3**). Compound **2d**, in the presence of sulfuric acid, easily reacted with a series of ketones and aldehydes to give 4*H*-2,2-disubstituted-6-alkylthio-5-cyano-2,3-dihydro-1,3-thiazin-4-ones.



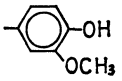
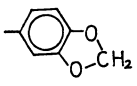
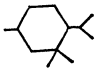
1 **2**

1a, **2a**: R=CN; **1b**, **2b**: R=CO_2CH_3; **1c**, **2c**: R=$CO_2C_2H_5$; **1d**, **2d**$_1$: R=$CONH_2$

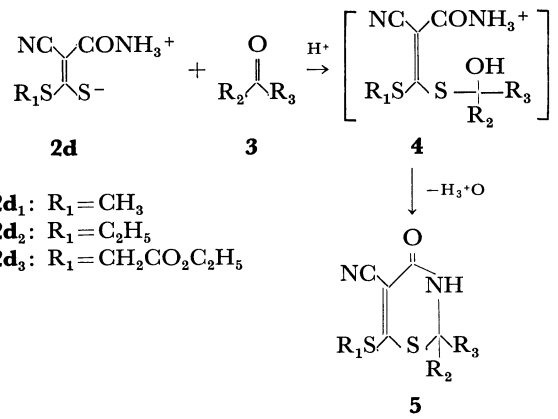
Scheme 1

The formation of **5** was considered to proceed through an intermediate **4** in the reaction of **2d** with **3**, because β,β-bis(methylthio)-α-cyanoacrylamide and **3** did not react in the presence of sulfuric acid to give *N*-addition

Table 1. Appearance, melting points, and yields

Compd.	R_1	R_2	R_3	Apperance	Mp, °C(cor)	Yield, %
5a	CH_3	R_2, $R_3=(CH_2)_5$		C. P.	227—228	93
5b	CH_3	R_2, $R_3=(CH_2)_4$		C. N.	190—191	88
5c	CH_3	CH_3	CH_3	C. N.	197—198	92
5d	CH_3	CH_3	C_2H_5	C. P.	187—188	93
5e	CH_3	H	CH_3	C. P.	212—213	90
5f	CH_3	H	C_6H_5	C. P.	225—226	92
5g	CH_3	H		C. N.	241—242 (dec)	95
5h	CH_3	H		C. N.	208—209	89
5i	CH_3	H		B. Pr.	213—214 (dec)	90
5j	C_2H_5	R_2, $R_3=(CH_2)_5$		C. N.	188—189	93
5k	C_2H_5	CH_3	CH_3	C. N.	151—152	91
5l	C_2H_5	H	CH_3	C. N.	172—173	87
5m	C_2H_5	H	C_6H_5	C. N.	177—178	95
5n	C_2H_5	H		B. N.	181—182 (dec)	92
5o	$CH_2CO_2CH_3$	R_2, $R_3=(CH_2)_5$		C. N.	138—139	82
5p	$CH_2CO_2CH_3$	H	CH_3	C. N.	169—170	83
5q	$CH_2CO_2CH_3$	H	C_6H_5	C. Pr.	151—152	80
5r	$CH_2CO_2CH_3$	R_2, R_3=		C. N.	152—153	76

C. P.: colorless plates; C.N.: colorless needles; C. Pr.: colorless prisms; B. N.: brown needles; B. Pr.: brown prisms



2d **3** **4**

2d$_1$: $R_1=CH_3$
2d$_2$: $R_1=C_2H_5$
2d$_3$: $R_1=CH_2CO_2C_2H_5$

Scheme 2.

TABLE 2. MASS SPECTRA FOR **5**[a], *m/e* (rel. int. %)

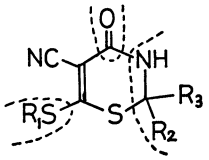
5c	**5d**
214 (M^+, 50)	228 (M^+, 67)
199 (42, $-CH_3$)	213 (13, $-CH_3$)
167 (92. $-SCH_3$)	199 (67, $-C_2H_5$)
157 (25, $-NHC(CH_3)_2$)	181 (100, $-SCH_3$)
110 (100)	157 (26, $-NHC(CH_3)(C_2H_5)$)
82 (33)	110 (83)
	82 (26)
5e	**5f**
200 (M^+, 93)	262 (M^+, 36)
185 (67, $-CH_3$)	215 (86, $-SCH_3$)
157 (60, $-NHCHCH_3$)	185 (15, $-C_6H_5$)
153 (67, $-SCH_3$)	157 (17, $-NHCHC_6H_5$)
110 (100)	110 (100)
82 (27)	82 (21)
5i	**5k**
252 (M^+, 44)	228 (M^+, 40)
205 (100, $-SCH_3$)	213 (100, $-CH_3$)
157 (13, $-NHCH(C_4H_3O)$)	200 (10, $-CO$)
110 (88)	171 (40, $-NHC(CH_3)_2$)
82 (25)	167 (90, $-SC_2H_5$)
	143 (40)
	110 (90)
	82 (40)
5l	**5m**
214 (M^+, 63)	276 (M^+, 62)
199 (100, $-CH_3$)	261 (13, $-CH_3$)
186 (15, $-CO$)	248 (17, $-CO$)
171 (37, $-NHCHCH_3$)	215 (100, $-SC_2H_5$)
153 (37, $-SC_2H_5$)	199 (33, $-C_6H_5$)
143 (63)	171 (70, $-NHCHC_6H_5$)
110 (63)	143 (44)
82 (17)	110 (55)
	82 (44)

a) Mass spectra were measured with a Nihon Denshi JMS-01 SG mass spectrometer. Ionizing energy was maintained at 75 eV and the total ionizing current was 200 μA.

derivatives(Scheme 2).

Table 1 shows the appearance, melting points, and yields of **5** of the present method. The structure of **5** was determined by studying the reaction process and the results of elemental analysis (Table 6) and the IR, NMR and mass spectra. In this reaction, β-ethoxycarbonylmethylthio-β-mercapto-α-cyanoacrylamide (**2d$_3$**) was treated with methanol using as solvent in the presence of acidic catalyst and converted into 4*H*-2,2-disubstituted-5-cyano-2,3-dihydro-6-methoxycarbonylthio-1,3-thiazin-4-one (**5o—r**) by the ester interchange.

The NMR spectra of **5m** revealed a broad peak at δ8.30 characteristic for NH, and a peak of R_2 at δ6.20 was split by the effect of NH. The mass spectra of **5** showed four characteristic fragments (Table 2); (M—NHR_2R_3), (M—CO), (M—NHR_2R_3—SR_1), and (M—NHR_2R_3—SR_1—CO). The fragments were considered to be formed by the following fragmentation.



The derivatives of 4*H*-1,3-thiazin-4-one have previously been synthesized through the reaction of methyl β-thiocarbamoylthiopropionate with sulfuric acid,[1] of substituted thiosemicarbazides with dimethyl acetylenedicarboxylate,[2] and of *N*-substituted dithiocarbamic acid with propionic acid.[3] The 4*H*-1,3-thiazin-4-one derivatives hitherto reported have been 4*H*-5,6-dihydro-1,3-thiazin-4-ones. This is a new preparative method leading to 4*H*-2,3-dihydro-1,3-thiazin-4-one derivatives, which have not yet been reported. The UV spectra showed the absorption near 225 mμ corresponding to the π—π^* of the carbonyl group and near 275 mμ corresponding to the π—π^* of the double bond (Table 3).

TABLE 3. UV SPECTRA OF **5**[a]

Compd.	λ_{max}, mμ (log ε), in 99% EtOH
5a	226 (sh, 2.68), 239 (sh, 3.79), 275 (3.51), 332 (3.57)
5d	230 (sh, 3.26), 273 (3.83), 332 (3.90)
5g	230 (3.23), 285 (2.90), 343 (3.08)
5h	231 (3.96), 286.5 (3.90), 342 (4.02)
5k	225 (sh, 3.40), 276 (3.78), 330 (3.91)
5m	230 (sh, 3.92), 280.5 (3.99), 335 (4.03)
5n	225.5 (sh, 3.89), 287.5 (3.62), 335.5 (3.79)
5**r**	220.5 (4.26), 289 (4.08), 342 (4.47)

a) The absorbance measurements were made with a Hitachi EPS-3T type spectrophotometer.

Experimental

Microanalyses were performed at the Institute of Physical and Chemical Research. The NMR data are given in the

1) J. E. Jansen and R. A. Mathes, *J. Amer. Chem. Soc.*, **77**, 2866 (1955).
2) J. W. Lown and J. C. N. Ma, *Can. J. Chem.*, **45**, 953 (1967).
3) R. N. Warrener and E. N. Cain, *Chem. Ind.*, **1964**, 48.

order of multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet), integration, and assignment.

Preparation of β,β-Dimercapto-α-cyanoacrylonitrile (1a), Methyl β,β-Dimercapto-α-cyanoacrylate (1b), Ethyl β,β-Dimercapto-α-cyanoacrylate (1c), and β,β-Dimercapto-α-cyanoacrylamide (1d). Sodium salts of **1a**, **1b**, and **1c** were prepared by Gompper's method.[4] Ammonium salt of **1d** was prepared from the reaction of ethyl cyanoacetate, carbon disulfide, and aqueous ammonia.[5]

The alkylation of **1a**, **1b**, **1c**, and **1d** was worked up with dimethyl sulfate and diethyl sulfate in the usual way.

Conversion of 1d into β-Alkylthio-β-mercaptoacrylamide (2d). To a mixture of diammonium salt of **1d** (21 g, 0.11 mol) and methanol (100 m*l*) was added dimethyl sulfate (10 m*l*, 0.11 mol) slowly under stirring below 20°C. The reaction mixture was allowed to stand for 8 hr and poured into water (500 m*l*). The yellow solution was acidified with concentrated hydrochloric acid (30 m*l*). The colorless material was collected by filtration, washed with dilute hydrochloric acid, dried, and recrystallized from methanol to give ca. 18 g of colorless needles (β-methylthio-β-mercapto-α-cyanoacrylamide, **2d**$_1$): yield 95%; mp 149—150°C (dec) (reported mp 145—146°C (dec)[4]). The IR spectrum coincided with that of the compound which was prepared from potassium hydroxide, cyanoacetamide, carbon disulfide, and methyl iodide by Gompper's method.[4]

The ethylation of **1d** was worked up as mentioned in the methylation of **1d**. The crude material was recrystallized from methanol - water to give colorless needles (β-ethylthio-β-mercapto-α-cyanoacrylamide, **2d**$_2$): yield 98%; mp 116—117°C (dec); UV$_{max}$ (99% EtOH): 227 mμ (log ε 4.16), 292.5 (3.97), 343 (4.01); Mass spectrum (75 eV) *m/e* (rel. intensity): 188 (100, M^+), 171 (20, $-NH_3$), 160 (13, –CO), 127 (73, $-SC_2H_5$); IR (KBr): 3420, 3280, 3180 (NH_3^+), 2980, 2920 (CH), 2200 (conj. CN), 1650 (CO), 1550 (conj. C=C), 1450 cm^{-1} (CH); NMR (DMSO-d_6) δ: 7.75 (broad, 3H, NH_3^+), 3.15 (q, 2H, CH_2, J=7 Hz), 1.42 (t, 3H, CH_3, J=7 Hz). Found: C, 38.19; H, 3.99; N, 14.93; S, 33.98%; mol wt (mass), 188. Calcd for $C_6H_8N_2S_2O$: C, 38.29; H, 4.25; N, 14.88; S, 34.07%; mol wt, 188.18.

The preparation of β-ethoxycarbonylmethylthio-β-mercapto-α-cyanoacrylamide (**2d**$_3$) was worked up as follows. To a mixture of potassium hydroxide (22.4 g, 0.4 mol) and methanol (120 m*l*) was added cyanoacetamide (16.8 g, 0.2 mol) and then carbon disulfide (12 m*l*) under cooling below 20°C. Ethyl bromoacetate (22 m*l*, 0.2 mol) was added slowly to the reaction mixture under cooling below 20°C. The mixture was allowed to stand for 5 min at 0°C, poured into water (500 m*l*), and acidified with concentrated hydrochloric acid (30 m*l*) to give a colorless precipitation. The crude product was collected by filtration, washed with dilute hydrochloric acid, dried, and recrystallized from methanol to give 30 g of colorless prisms: yield 65%; mp 138—139°C (dec); UV$_{max}$ (99% EtOH): 220 mμ (sh, log ε 4.02), 277.5 (3.78), 334 (3.87); Mass spectrum (75 eV) *m/e* (rel. intensity): 246 (27, M^+), 232 (40, $-CH_2$), 215 (8, $-NH_3$), 200 (50, $-C_2H_5$, $-NH_3$), 127 (100, $-SCH_2CO_2C_2H_5$); IR (KBr): 3320, 3240, 316 (NH_3^+), 2960 (CH), 2200 (conj. CN), 1730 ($COOC_2H_5$), 1655 (CO), 1530 (conj. C=C), 1485 (CH), 1298 cm^{-1} (C–O–C). Found: C, 38.91; H, 4.04; N, 11.11; S, 26.20%; mol wt (mass), 246. Calcd for $C_8H_{10}N_2S_2O_3$; C, 39.03; T, 4.06; N, 11.37; S, 26.04%; mol wt, 246.20.

Preparation of 4H-5-*cyano*-2,3-*dihydro*-6-*methylthio*-1,3-*thiazin*-4-*one*-2-*spirocyclohexane (5a).* A mixture of cyclohexanone (5 g, 0.05 mol), β-methylthio-β-mercapto-α-cyanoacrylamide (3 g, 0.02 mol), 2% sulfuric acid (10 m*l*), and methanol (50 m*l*) was refluxed for 10 min. The crude material was collected by filtration, washed with methanol, dried, and recrystallized from acetic acid to give 4 g of colorless plates (**5a**); IR (KBr): 3280, 3160, 3040 (NH), 2900 (CH), 2220 (conj. CN), 1650 (CO), 1470 cm^{-1} (CH); NMR (CF_3CO_2H)δ: 8.30 (broad, 1H, NH), 2.78 (s, 3H, SCH_3), 2.20 (m, 4H, $2CH_2$), 1.75 (m, 6H, $3CH_2$). Found: C, 51.74; H, 5.48; N, 10.95; S, 25.19%; mol wt (mass), 254. Calcd for $C_{11}H_{14}N_2S_2O$: C, 51.96; H, 5.50; N, 11.01; S, 25.22%; mol wt, 254.23.

The preparations of **5b** to **5r** were worked up as mentioned in the isolation of **5a**. The appearance, melting

Table 4. IR (KBr) data of **5**, cm^{-1}

5d	3260, 3160, 3040 (NH), 2980, 2920 (CH), 2220 (CN), 1645 (CO), 1465 (CH)
5g	3320, 3280, 3180 (NH), 3040 (arom. CH), 2980 (CH), 2220 (CN), 1650 (CO), 1620, 1515 (benzene ring), 1470 (CH)
5h	3240, 3160, 3040 (NH, arom. CH), 2860 (CH), 2240 (CN), 1660 (CO), 1500 (benzene ring), 1480 (CH)
5k	3280, 3160, 3040 (NH), 2900 (CH), 2220 (CN), 1655 (CO), 1470 (CH)
5m	3320, 3250 (NH), 2980 (CH), 2220 (CN), 1670 (CO), 1620 (benzene ring), 1470 (CH)
5n	3300 (NH), 2970 (CH), 2220 (CN), 1670 (CO), 1620 (furan ring), 1470 (CH)
5r	3420, 3350, 3200 (NH), 2960, 2940 (CH), 2220 (CN), 1720 (CO_2CH_3), 1670 (CO)

Table 5. NMR (in CF_3CO_2H) data of **5**, δ value

5d	8.42 (broad, 1H, NH), 2.80 (s, 3H, SCH_3), 2.20 (q, 2H, CH_2CH_3, J=7 Hz), 1.85 (s, 3H, CH_3), 1.15 (*t*, 3H, CH_2CH_3, J=7 Hz)
5g	8.35 (broad, 1H, NH), 7.23 (s, 1H, C_6H_5), 7.15 (s, 2H, C_6H_5), 6.10 (s, 1H, CH), 3.95 (s, 3H, OCH_3), 2.70 (s, 3H, SCH_3)
5h	8.30 (broad, 1H, NH), 7.08 (s, 2H, CH_2), 6.98 (s, 1H, CH), 6.05 (s, 3H, C_6H_3), 2.80 (s, 3H, SCH_3)
5k	8.40 (broad, 1H, NH), 3.35 (q, 2H, CH_2CH_3, J=7 Hz), 1.90 (s, 6H, $2CH_3$), 1.50 (t, 3H, CH_2CH_3, J=7 Hz)
5m	8.30 (broad, 1H, NH), 7.50 (s, 5H, C_6H_5), 6.15 (d, 1H, H), 3.30 (q, 2H, CH_2), 1.45 (t, 3H, CH_3)
5n	8.50 (broad, 1H, NH), 7.55 (d, 1H, C_4H_3O, J=4 Hz), 6.70 (d, 1H, C_4H_3O, J_{34}=7Hz), 6.50 (q, 1H, C_4H_3O, J_{45}=4Hz, J_{34}=7Hz), 6.30 (s, 1H, CH), 3.35 (q, 2H, CH_2CH_3, J=7 Hz), 1.53 (t, 3H, CH_2CH_3, J=7 Hz)
5r	7.10 (broad, 1H, NH), 4.35 (s, 2H, C(6′)H_2), 4.30 (s, 6H, C(2′, 5′)H, C(3′, 4′)H_2), 4.20 (s, 2H, SCH_2CO_2), 4.05 (s, 9H, $3CH_3$), 3.90 (s, 3H, CO_2CH_3), 3.65 (s, 1H, CH)

4) R. Gompper and W. Töpfel, *Chem. Ber.*, **95**, 2861 (1962).
5) M. Yokoyama, This Bulletin, **43**, 2938 (1970).

TABLE 6. ANALYSES OF **5**

Compd.	Formula	Calcd (%)				Found (%)			
		C	H	N	S	C	H	N	S
5b	$C_{10}H_{12}N_2S_2O$	49.99,	5.00,	11.66,	26.69	50.18,	4.74,	11.69,	26.75
5c	$C_8H_{10}N_2S_2O$	44.86,	4.67,	13.07,	29.93	44.70,	4.77,	13.16,	29.87
5d	$C_9H_{12}N_2S_2O$	47.36,	5.26,	12.27,	28.10	47.21,	5.10,	12.37,	28.12
5e	$C_7H_8N_2S_2O$	41.99,	3.99,	13.99,	32.03	42.05,	4.03,	13.91,	31.85
5f	$C_{12}H_{10}N_2S_2O$	54.96,	3.81,	10.68,	24.45	54.81,	3.91,	10.57,	24.25
5g	$C_{13}H_{12}N_2S_2O_3$	50.65,	3.89,	9.08,	20.80	50.89,	3.93,	9.16,	20.56
5h	$C_{13}H_{10}N_2S_2O_3$	50.98,	3.27,	9.14,	20.94	50.88,	3.07,	9.02,	20.71
5i	$C_{10}H_8N_2S_2O_2$	47.62,	3.17,	11.10,	25.42	47.63,	3.11,	10.94,	25.35
5j	$C_{12}H_{16}N_2S_2O$	53.72,	5.96,	10.44,	23.90	53.68,	5.69,	10.31,	23.66
5k	$C_9H_{12}N_2S_2O$	47.36,	5.26,	12.27,	28.10	47.24,	5.10,	12.39,	27.91
5l	$C_8H_{10}N_2S_2O$	44.86,	4.67,	13.07,	29.93	44.65,	4.49,	13.14,	29.64
5m	$C_{13}H_{12}N_2S_2O$	56.52,	4.34,	10.14,	23.21	56.42,	4.71,	10.22,	23.20
5n	$C_{11}H_{10}N_2S_2O_2$	49.62,	3.76,	10.52,	24.08	49.55,	3.57,	10.47,	23.99
5o	$C_{13}H_{16}N_2S_2O_3$	50.04,	5.12,	8.97,	20.55	50.00,	5.22,	8.89,	20.51
5p	$C_8H_8N_2S_2O_3$	39.34,	3.28,	11.47,	26.26	39.25,	3.42,	11.53,	26.20
5q	$C_{13}H_{10}N_2S_2O_3$	50.98,	3.27,	9.14,	20.94	50.96,	3.18,	9.08,	20.99
5r	$C_{16}H_{22}N_2S_2O_3$	54.24,	6.21,	7.90,	18.10	54.33,	6.15,	8.03,	18.16

points, and yields of **5a** to **5r** were included in Table 1. Tables 2 and 3 showed Mass and UV spectra for the typical compounds of **5**. Compound **5**, generally, was easily soluble in concentrated sulfuric acid and acetic acid. The IR and NMR spectra for the typical compounds of **5** were shown in Tables 4 and 5.

Compounds **5** synthesized were: 4*H*-5-cyano-2,3-dihydro-6-methylthio-1,3-thiazin-4-one-2-spirocyclopentane (**5b**), 4*H*-5-cyano-2,3-dihydro-2,2-dimethyl-6-methylthio-1,3-thiazin-4-one (**5c**), 4*H*-5-cyano-2,3-dihydro-2-ethyl-2-methyl-6-methylthio-1,3-thiazin-4-one (**5d**), 4*H*-5-cyano-2,3-dihydro-2-methyl-6-methylthio-1,3-thiazin-4-one (**5e**), 4*H*-5-cyano-2,3-dihydro-6-methylthio-2-phenyl-1,3-thiazin-4-one (**5f**), 4*H*-5-cyano-2,3-dihydro-2-(3-methoxy-4-hydroxyphenyl)-6-methylthio-1,3-thiazin-4-one (**5 g**), 4*H*-5-cyano-2,3-dihydro-2-(3,4-methylenedioxyphenyl)-6-methylthio-1,3-thiazin-4-one (**5h**), 4*H*-5-cyano-2,3-dihydro-2-furyl-6-methylthio-1,3-thiazin-4-one (**5i**), 4*H*-5-cyano-2,3-dihydro-6-ethylthio-1,3-thiazin-4-one-2-spirohexane (**5j**), 4*H*-5-cyano-2,3-dihydro-2,2-dimethyl-6-ethylthio-1,3-thiazin-4-one(**5k**), 4*H*-5-cyano-2,3-dihydro-6-ethylthio-2-methyl-1,3-thiazin-4-one(**5l**), 4*H*-5-cyano-2,3-dihydro-6-ethylthio-2-phenyl-1,3-thiazin-4-one(**5m**), 4*H*-5-cyano-2,3-dihydro-6-ethylthio-2-furyl-1,3-thiazin-4-one(**5n**), 4*H*-5-cyano-2,3-dihydro-6-methoxycarbonylmethylthio-1,3-thiazin-2-spirohexane(**5o**), 4*H*-5-cyano-2,3-dihydro-6-methoxycarbonylmethylthio-2-methyl-1,3-thiazin-4-one(**5p**), 4*H*-5-cyano-2,3-dihydro-6-methoxycarbonylmethylthio-2-phenyl-1,3-thiazin-4-one(**5q**), and 4*H*-5-cyano-2,3-dihydro-6-methoxycarbonylmethylthio-1,3-thiazin-4-one-2-spiro-2′-(1-isopropyl-4-methylcyclohexane)(**5r**), respectively.

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