FORMATION AND REACTION OF MESOIONIC IMIDAZOLO[2,3-b][1,3]THIAZINES AND [1,2,4,6]THIATRIAZINO[3,2-b][1,3]THIAZIN-4-ONE 2,2-DIOXIDES FROM 2-ARYLIMINO-1,3-THIAZINES

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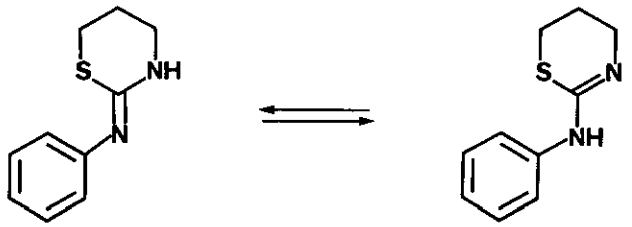
Abstract — Two regioisomers of mesoionic imidazolones, obtained from the reaction of 2-arylimino-1,3-thiazines with chloroacetyl chloride (CAC), gave pyridones or pyrroles upon reaction with dimethyl acetylenedicarboxylate (DMAD). Also, 2-arylimino-1,3-thiazines gave mesoionic 1,2,4,6-thiatriazin-3-one 1,1-dioxides by reaction with chlorosulfonyl isocyanate (CSI), although only one regioisomer was obtained.

2-Phenylimino-1,3-thiazine A can exist in the tautomeric form B, and the predominant tautomeric form has been shown to be the imino form A in solution by ^{1}H and ^{13}C nmr chemical shifts[1,2]. And 2-arylimino-1,3-thiazines behave as ambident nucleophiles toward electrophiles because of having two nitrogen atoms. In the present paper, we describe the formation and reaction of mesoionic heterocycles from 2-arylimino-1,3-thiazines.



A B

The reaction of 1a-e with CAC in the presence of pyridine gave two regioisomers of mesoionic imidazolones 2a-e and 3a-e (Table 1). Synthesis of mesoionic 2-acetyl-

1-methylimidazolones from thiohydantoin has been reported by Barton[3]. Support for the proposed structures of 2a-e and 3a-e came from the spectral data and chemical transformation.

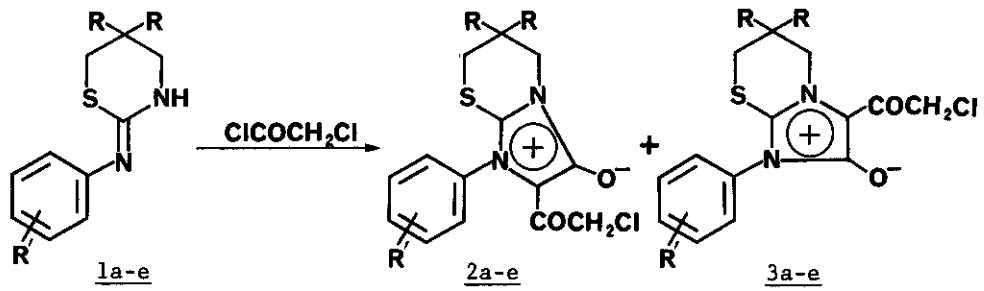
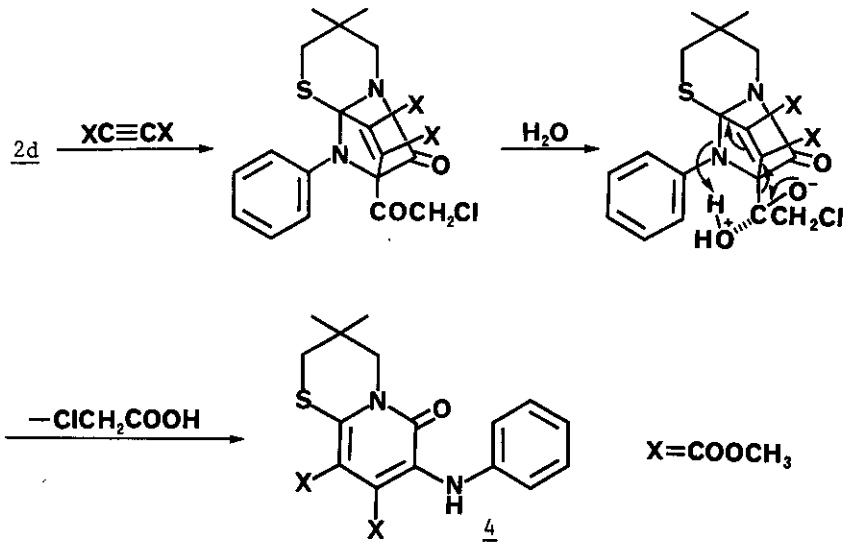


Table 1. Reactions of 1a-e with chloroacetyl chloride

Compound	R	R'	Yield(%) 2	Yield(%) 3
1a	CH_3	4-n-Bu	32	20
1b	CH_3	2-CH_3-4-Cl	44	42
1c	H	2-CH_3-4-Cl	33	40
1d	CH_3	H	59	39
1e	H	H	15	50

The structures of 2a-e and 3a-e were assigned on the basis of their ^{1}H nmr spectra. These regioisomers showed remarkably different ^{1}H nmr chemical shifts of the C_5-



Scheme 1

proton: 3.59-3.93 ppm and 4.36-4.62 ppm for 2a-e and 3a-e, respectively. The distinct downfield shift of the C_5-proton in 3a-e is due to the carbonyl double bond. The mesoionic 1,3-thiazol-4-ones undergo so-called 1,4-cycloaddition to produce pyridones by sulfur extrusion[7]. The reaction of 2d with DMAD in DMF at room temperature produced 7-anilino-8,9-dimethoxycarbonyl-3,3-dimethyl-6-oxopyrido-[2,1-b][1,3]thiazine 4, in 21% yield. For the mechanism of this reaction, we postulate that the pyridone results from hydrolytic loss of the chloroacetyl group from the 1,3-cycloaddition product (Scheme 1). Compound 4 had the stretching band of the cyclic amide carbonyl at 1630 cm^{-1} and ^1H nmr signals for aromatic protons. The reaction of 3b,d,e with DMAD under the same conditions led to 1,3-cycloaddition to give the pyrrolo[2,1-b][1,3]thiazines 5b,e (3b and 3d gave the same product, 5b) by elimination of aryl isocyanate from the adduct (Table 2).

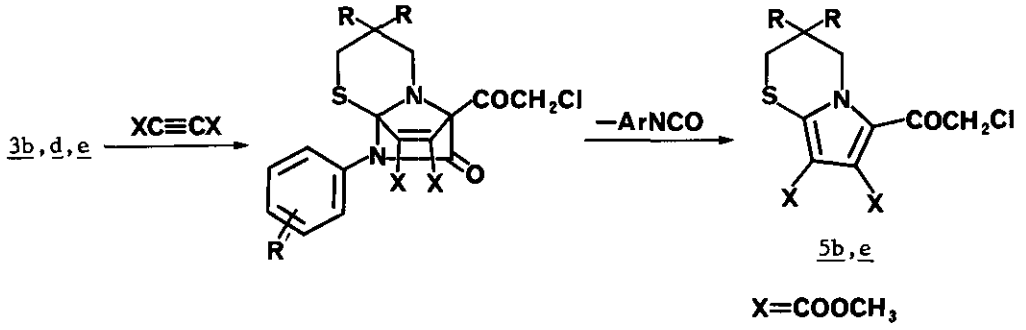
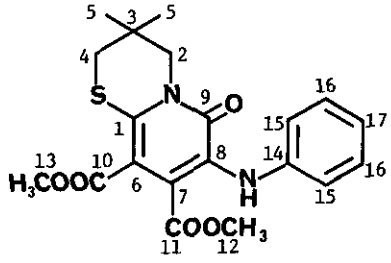


Table 2. Reactions of 3b,d,e with DMAD

Compound	R	R'	Yield(%) 5
3b	CH_3	2-CH_3-4-Cl	96
3d	CH_3	H	45
3e	H	H	83

Compounds 5b,e had the stretching band of the conjugated ketone at 1670 cm^{-1} and 1675 cm^{-1}, respectively. The ^{13}C nmr spectra supported these structures (Table 3). On the other hand, the reaction of 1a,c,d with CSI proceeded regio-selectively, and gave the mesoionic compounds 6a,c,d (Table 4) as described by Friedrichsen[4] and Karady[5] for the reaction of amidines with CSI. In this case, the structures were not confirmed by ^1H nmr spectra or chemical approaches. The structure of 6a was finally confirmed by X-ray evidence[6] (Fig. 1), and the structures of 6c,d



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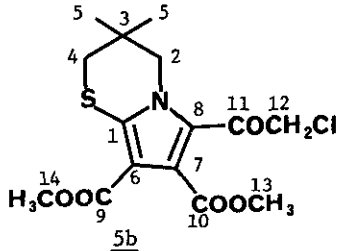
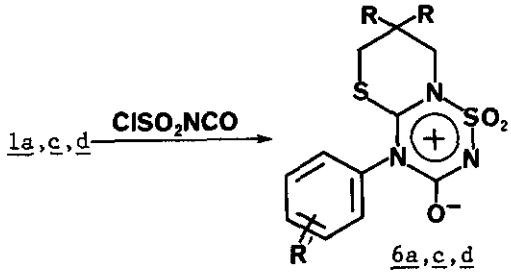


5b

Table 3. ^{13}C Nmr spectra of 4 and 5b

	δ ppm (in $CDCl_3$)	
	4	5b
C-1	135.2 (s)	137.9 (s)
C-2	53.4 (t)	56.6 (t)
C-3	35.2 (s)	29.2 (s)
C-4	40.3 (t)	36.0 (t)
C-5	26.6 (q)	25.5 (q)
C-6	111.9 (s)	110.3 (s)
C-7	117.7 (s)	126.5 (s)
C-8	130.1 (s)	126.5 (s)
C-9	159.7 (s)	166.8 (s)
C-10	166.2 (s)**	162.7 (s)
C-11	166.0 (s)**	180.8 (s)
C-12	52.5 (q)*	46.8 (t)
C-13	51.9 (q)*	51.8 (q)*
C-14	141.4 (s)	53.3 (q)*
C-15	120.6 (d)	
C-16	129.0 (d)	
C-17	123.4 (d)	

*,** Assignments may be reversed.



6a,c,d

Table 4. Reactions of 1a,c,d with CSI

Compound	Yield(%) 6
1a	90
1c	83
1d	94

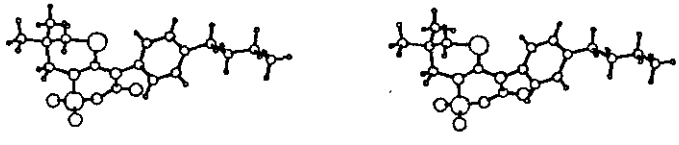


Fig. 1. Stereoscopic view of compound 6a

were assigned from comparison of ^{13}C nmr spectra. These structures showed that the isocyanate reacted with the exo nitrogen atom. Compounds 6a,d showed the same ^{13}C nmr chemical shift of CH_2N, 53.2 ppm, and that of 6c was at 44.2 ppm. The difference of values between 6a,c,d and 2a,b,e shows that the nitrogen atom of CH_2N in 6a,c,d is connected with the sulfonyl group instead of the carbonyl group (Table 5).

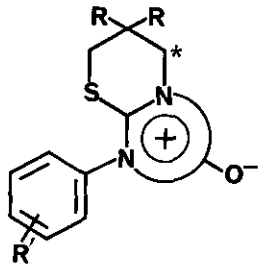


Table 5. ^{13}C Nmr chemical shifts of $\overset{*}{C}H_2N$

Compound	δ ppm
2a	49.4 (2)
2b	48.5 (1)
2e	38.6 (1), 38.9 (2)
3a	55.6 (2)
3b	54.8 (1)
3e	45.3 (1)
6a	53.2 (1)
6c	44.2 (1)
6d	53.2 (1)

Solvent used: (1) DMSO-d_6, (2) $CDCl_3$

EXPERIMENTAL

All melting points are uncorrected. ^1H and ^{13}C nmr spectra were obtained on a JEOL JNM-PMX 60Si spectrometer or Varian XL-100 spectrometer with TMS as the internal standard. Ir spectra were measured on a Hitachi 260-10 infrared spectrometer. Mass spectra were measured on a Hitachi RMU-8GN mass spectrometer.

General Method for Preparation of 2-Chloroacetylimidazolo[2,3-b][1,3]thiazinylium-3-olate (2a-e) and 3-Chloroacetylimidazolo[2,3-b][1,3]thiazinylium-2-olate (3a-e). To a solution of the 2-arylimino-1,3-thiazine 1a-e (0.01 mol) and pyridine (0.07 mol) in methylene chloride (30 ml, except for 1e, which was in chloroform), chloroacetyl chloride (0.05 mol) was added dropwise at 0°C with stirring. After 30 min, the reaction mixture was washed with 1 N hydrochloric acid, sat. sodium hydrogen carbonate, and brine, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel. The fraction eluted with ethyl acetate gave 3a-e and the second fraction eluted with acetone gave 2a-e, in the yields shown in Table 1.

1-(4-n-Butylphenyl)-2-chloroacetyl-6,7-dihydro-6,6-dimethyl-5H-imidazolo[2,3-b]-[1,3]thiazinylium-3-olate (2a) – Mp 185-188.5°C (decomp.) (from benzene-n-hexane); ir ($CHCl_3$) 1615 (C=C), 1675 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 0.93 (3H,t,J=7Hz), 1.0-1.8 (4H,m), 1.20 (6H,s), 2.67 (2H,t,J=7Hz), 2.93 (2H,s), 3.60 (2H,s), 4.65 (2H,s), 7.23 (4H,s); ms m/z: 392 (M^+); (Found: C, 60.86; H, 6.30; N, 7.15. Calcd. for $C_{20}H_{25}ClN_2O_2S$: C, 61.13; H, 6.41; N, 7.13%).

2-Chloroacetyl-6,7-dihydro-6,6-dimethyl-1-(2-methyl-4-chlorophenyl)-5H-imidazolo-[2,3-b][1,3]thiazinylium-3-olate (2b) – Mp 206-207°C (decomp.) (from benzene-n-hexane); ir ($CHCl_3$) 1608 (C=C), 1670 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 1.20 (3H,s), 1.24 (3H,s), 2.07 (3H,s), 2.91 (2H,s), 3.60 (2H,dd,J=16,14Hz), 4.60 (2H,s), 7.0-7.3 (3H,m); ms m/z: 384 (M^+); (Found: C, 52.93; H, 4.72; N, 7.27. Calcd. for $C_{17}H_{18}Cl_2N_2O_2S$: C, 52.99; H, 4.71; N, 7.27%).

2-Chloroacetyl-6,7-dihydro-1-(2-methyl-4-chlorophenyl)-5H-imidazolo[2,3-b][1,3]-thiazinylium-3-olate (2c) – Mp 177-179°C (decomp.) (from benzene); ir ($CHCl_3$) 1610 (C=C), 1670 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 2.15 (3H,s), 2.34 (2H,m), 3.23 (2H,t,J=6Hz), 3.93 (2H,t,J=6Hz), 4.57 (2H,s), 7.0-7.3 (3H,m); ms m/z: 356 (M^+); (Found: C, 50.56; H, 3.97; N, 7.75. Calcd. for $C_{15}H_{14}Cl_2N_2O_2S$: C, 50.43; H, 3.95; N, 7.84%).

2-Chloroacetyl-6,7-dihydro-6,6-dimethyl-1-phenyl-5H-imidazolo[2,3-b][1,3]-thiazinylium-3-olate (2d) – Mp 203-205°C (decomp.) (from benzene); ir ($CHCl_3$) 1615 (C=C), 1675 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 1.21 (6H,s), 2.93 (2H,s), 3.59 (2H,s), 4.63 (2H,s), 7.3-7.6 (5H,m); ms m/z: 336 (M^+); (Found: C, 57.28; H, 5.08; N, 8.24. Calcd. for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.32%).

2-Chloroacetyl-6,7-dihydro-1-phenyl-5H-imidazolo[2,3-b][1,3]thiazinylium-3-olate (2e) – Mp 215-216°C (decomp.) (from benzene-n-hexane); ir ($CHCl_3$) 1615 (C=C), 1670 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 2.33 (2H,m), 3.17 (2H,t,J=6Hz), 3.93 (2H,t,J=7Hz), 4.64 (2H,s), 7.2-7.6 (5H,m); ms m/z: 308 (M^+); (Found: C, 54.07; H, 4.26; N, 9.03. Calcd. for $C_{14}H_{13}ClN_2O_2S$: C, 54.46; H, 4.24; N, 9.07%).

1-(4-n-Butylphenyl)-3-chloroacetyl-6,7-dihydro-6,6-dimethyl-5H-imidazolo[2,3-b][1,3]-thiazinylium-2-olate (3a) – Mp 135-137.5°C (decomp.) (from benzene-n-hexane); ir ($CHCl_3$) 1605 (C=C), 1680 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 0.93 (3H,t,J=7Hz), 1.0-1.8 (4H,m), 1.22 (6H,s), 2.67 (2H,t,J=7Hz), 2.93 (2H,s), 4.36 (2H,s), 4.69 (2H,s), 7.27 (4H,s); ms m/z: 392 (M^+); (Found: C, 61.40; H, 6.53; N, 6.74. Calcd. for $C_{20}H_{25}ClN_2O_2S$: C, 61.13; H, 6.41; N, 7.13%).

3-Chloroacetyl-6,7-dihydro-6,6-dimethyl-1-(2-methyl-4-chlorophenyl)-5H-imidazolo-[2,3-b][1,3]thiazinylium-2-olate (3b) – Mp 174-177°C (decomp.) (from benzene); ir ($CHCl_3$) 1600 (C=C), 1680 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 1.25 (6H,s), 2.20 (3H,s), 2.95 (2H,s), 4.41 (2H,dd,J=16,14Hz), 4.68 (2H,s), 7.1-7.4 (3H,m); ms m/z: 384 (M^+); (Found: C, 52.92; H, 4.74; N, 7.27. Calcd. for $C_{17}H_{18}Cl_2N_2O_2S$: C, 52.99; H, 4.71; N, 7.27%).

3-Chloroacetyl-6,7-dihydro-1-(2-methyl-4-chlorophenyl)-5H-imidazolo[2,3-b][1,3]-

thiazinylium-2-olate (3c) – Mp 98-101°C (from benzene-n-hexane); ir ($CHCl_3$) 1600 (C=C), 1680 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 2.20 (3H,s), 2.40 (2H,m), 3.23 (2H,t,J=6Hz), 4.62 (2H,t,J=6Hz), 4.65 (2H,s), 7.0-7.4 (3H,m); ms m/z: 356 (M^+); (Found: C, 50.27; H, 4.02; N, 7.78. Calcd. for $C_{15}H_{14}Cl_2N_2O_2S$: C, 50.43; H, 3.95; N, 7.84%).

3-Chloroacetyl-6,7-dihydro-6,6-dimethyl-1-phenyl-5H-imidazolo[2,3-b][1,3]-thiazinylium-2-olate (3d) – Mp 277°C (decomp.) (from benzene-n-hexane); ir ($CHCl_3$) 1610 (C=C), 1670 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 1.23 (6H,s), 2.95 (2H,s), 4.39 (2H,s), 4.69 (2H,s), 7.3-7.6 (5H,m); ms m/z: 336 (M^+); (Found: C, 57.28; H, 5.02; N, 8.23. Calcd. for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.32%).

3-Chloroacetyl-6,7-dihydro-1-phenyl-5H-imidazolo[2,3-b][1,3]thiazinylium-2-olate (3e) – Mp 206-209°C (decomp.) (from benzene); ir ($CHCl_3$) 1610 (C=C), 1680 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 2.36 (2H,m), 3.20 (2H,t,J=6Hz), 4.65 (2H,t,J=6Hz), 4.70 (2H,s), 7.2-7.6 (5H,m); ms m/z: 308 (M^+); (Found: C, 54.87; H, 4.43; N, 9.12. Calcd. for $C_{14}H_{13}ClN_2O_2S$: C, 54.46; H, 4.24; N, 9.07%).

7-Anilino-3,4-dihydro-8,9-dimethoxycarbonyl-3,3-dimethyl-6-oxo-2H-pyrido[2,1-b]-[1,3]thiazine (4). A mixture of 2d (0.39 g) and DMAD (0.17 g) in DMF (2 ml) was stirred at room temperature for 1 day. After removal of the solvent, the residue was extracted with chloroform and the extract was chromatographed on silica gel with chloroform, giving 4 (0.10 g, 21%), mp 157-158.5°C (from n-hexane); ir ($CHCl_3$) 3350 (NH) 1730, 1722, 1630 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 1.13 (6H,s), 2.65 (2H,s), 3.31 (3H,s), 3.80 (3H,s), 4.07 (2H,s), 6.8-7.5 (6H,m); ms m/z: 402 (M^+); (Found: C, 59.50; H, 5.51; N, 6.94. Calcd. for $C_{20}H_{22}N_2O_5S$: C, 59.67; H, 5.51; N, 6.96%).

6-Chloroacetyl-3,4-dihydro-7,8-dimethoxycarbonyl-3,3-dimethyl-2H-pyrrolo[2,1-b]-[1,3]thiazine (5b). A mixture of 3b (0.50 g) and DMAD (0.19 g) in DMF (3 ml) was stirred at room temperature for 1 day. After removal of the solvent, the residue was extracted with chloroform and the extract was chromatographed on silica gel with chloroform, giving 5b (0.45 g, 96%), mp 118-121°C (from n-hexane); ir ($CHCl_3$) 1730, 1702, 1670 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 1.21 (6H,s), 2.85 (2H,s), 3.83 (3H,s), 3.95 (3H,s), 4.12 (2H,s), 4.40 (2H,s); ms m/z: 359 (M^+); (Found: C, 49.90; H, 4.91; N, 3.99. Calcd. for $C_{15}H_{18}ClNO_5S$: C, 50.07; H, 5.04; N, 3.89%).

6-Chloroacetyl-3,4-dihydro-7,8-dimethoxycarbonyl-2H-pyrrolo[2,1-b][1,3]thiazine (5e). A mixture of 3e (0.60 g) and DMAD (0.28 g) in DMF (4 ml) was stirred at room temperature for 5 h. After removal of the solvent, the residue was extracted with chloroform

and the extract was chromatographed on silica gel with chloroform, giving 5e (0.52 g, 83%), mp 136.5-137°C (from n-hexane); ir ($CHCl_3$) 1735, 1705, 1675 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 2.33 (2H,m), 3.04 (2H,t,J=6Hz), 3.80 (3H,s), 3.95 (3H,s), 4.40 (2H,s), 4.43 (2H,t,J=6Hz); ms m/z: 331 (M^+); (Found: C, 47.05; H, 4.28; N, 4.22. Calcd. for $C_{13}H_{14}ClNO_5S$: C, 47.06; H, 4.25; N, 4.22%).

General Method for Preparation of [1,2,4,6]Thiatriazino[3,2-b][1,3]thiazinylium-4-olate 2,2-Dioxide (6a,c,d). To a solution of the 2-arylimino-1,3-thiazine 1a,c,d (0.01 mol) and pyridine (0.07 mol) in methylene chloride (10 ml), chlorosulfonyl isocyanate (0.02 mol) was added dropwise at 0°C with stirring. After 10 min, 50 ml of water was added and the mixture was filtrated. Recrystallization from benzene gave 6a,c,d in the yields shown in Table 4.

5-(4-n-Butylphenyl)-8,9-dihydro-8,8-dimethyl-7H-[1,2,4,6]thiatriazino[3,2-b][1,3]-thiazinylium-4-olate 2,2-dioxide (6a) – Mp 203-205°C; ir (Nujol) 1340 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$)$_\delta$ 0.93 (3H,t,J=7Hz), 1.26 (6H,s), 1.2-1.8 (4H,m), 2.69 (2H,t,J=7Hz), 2.93 (2H,s), 3.90 (2H,s), 7.25 (4H,s); ms m/z: 381 (M^+); (Found: C, 53.30; H, 5.97; N, 10.65. Calcd. for $C_{17}H_{23}N_3O_3S_2$: C, 53.52; H, 6.08; N, 11.01%).

8,9-Dihydro-5-(2-methyl-4-chlorophenyl)-7H-[1,2,4,6]thiatriazino[3,2-b][1,3]-thiazinylium-4-olate 2,2-dioxide (6c) – Mp 205.5-208°C; ir (Nujol) 1338 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6)$_\delta$ 2.13 (3H,s), 2.17 (2H,m), 3.28 (2H,t,J=6Hz), 4.06 (2H,t,J=6Hz), 7.4-7.5 (3H,m); ms m/z: 345 (M^+); (Found: C, 41.45; H, 3.48; N, 11.92. Calcd. for $C_{12}H_{12}ClN_3O_3S_2$: C, 41.68; H, 3.50; N, 12.15%).

8,9-Dihydro-8,8-dimethyl-5-phenyl-7H-[1,2,4,6]thiatriazino[3,2-b][1,3]thiazinylium-4-olate 2,2-dioxide (6d) – Mp 203-206°C; ir (Nujol) 1340 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6)$_\delta$ 1.13 (6H,s), 3.10 (2H,s), 3.81 (2H,s), 7.4-7.6 (5H,m); ms m/z: 325 (M^+); (Found: C, 47.91; H, 4.53; N, 12.90. Calcd. for $C_{13}H_{15}N_3O_3S_2$: C, 47.98; H, 4.65; N, 12.91%).

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