2*H*-1,2,4,6-Thiatriazin-3(4*H*)-one 1-Oxides and Their Regioselective N^4-Methylation and -Amination

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The syntheses of 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides and 1,1-dioxides is described. The reaction of 1-carbamoyl-2-methylisothioureas **2** with thionyl chloride gave 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides **3** in high yields. The treatment of **3** with either diazomethane or *O*-(2,4-dinitrophenyl)hydroxylamine furnished regioselectively N^4-methylated and N^4-aminated 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides, respectively. Subsequent dimethylamination of **4** followed by oxidation with *m*-chloroperoxybenzoic acid led to 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1,1-dioxides **6a-c**.

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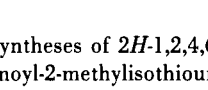
1,3,5-Triazine-2,4-diones are one of the most interesting chemical branches for the biological activities (for example, Hexazinone **1** is a potent herbicide) [2]. The replacement of carbonyl group in quinazoline derivatives with the SO_2 moiety has resulted in uniquely selective phytotoxic properties [3]. On the basis of this result, it was of interest to prepare the isosteres of 1,3,5-triazine-2,4-diones in which the 2-carbonyl was replaced by the bioisosteric SO and/or SO_2 groups. This communication reports a novel and convenient synthesis of 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides **3**. Regioselective N^4-methylation of **3** was clarified by the chemical conversions which have led to the formation of 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1,1-dioxides **6a-c**. Also, N^4-amination of **3** is described.



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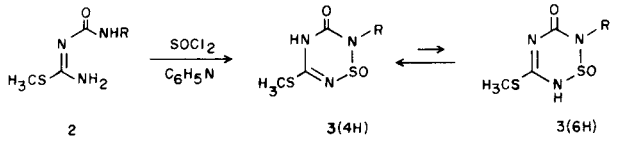
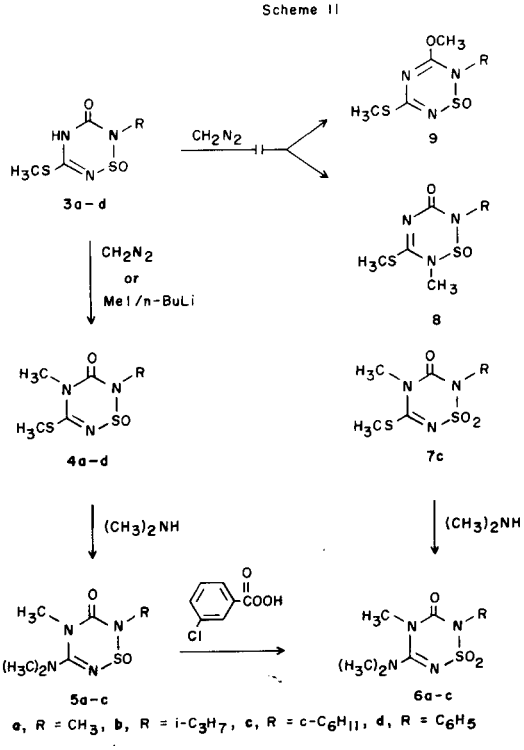
Scheme I



2 **3(4H)** **3(6H)**

The starting material of 1-carbamoyl-2-methylisothioureas **2** was readily prepared by the reaction of 2-methylisothiourea and isocyanates according to the reported method [4]. Here we discuss the reaction of **2** with thionyl chloride, sulfur dichloride and sulfuryl chloride. Thionyl chloride is one of the most common reagents used in the synthesis of heterocycles containing sulfur *via* condensation reactions [5]. The reaction of **2** with thionyl chloride proceeded smoothly in the presence of pyridine in chloroform yielding 5-methylthio-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides **3** in higher yields. The structure of **3** was determined on the basis of spectral evidences and analytical results listed in Table I. The presence of NH (3100-3200 cm^{-1}), CO (1690-1695 cm^{-1}) and SO (1100 cm^{-1}) groups was supported by the characteristic infrared absorptions. The M^+-SO peak is the base peak in the mass spectra of **3**. Attempted cyclization of **2** with sulfuryl dichloride resulted in a complex reaction mixture from which no identifiable products could be isolated. On the other hand, reaction of **2** with sulfuryl chloride under various conditions was unsuccessful, and in every instance starting material was almost recovered.

Scheme II



a, R = CH_3, **b**, R = i-C_3H_7, **c**, R = c-C_6H_{11}, **d**, R = C_6H_5

In spite of possible tautomerization between 3(4*H*) and 3(6*H*) forms, methylation of **3** with methyl iodide in the presence of *n*-butyllithium in tetrahydrofuran gave only product **4**. Compound **4** was also obtained upon treatment with diazomethane in higher yields (Table II). Theoretically, there should be three possibilities of methylation, at

Table I

Analytical and Spectral Data of 5-Methylthiothiatriazines **3**

Compound	Mp °C	Yield (%)	Formula	Analysis % Calcd. (Found) C	H	N	MS [a]	IR, cm^{-1} [b]	PMR (δ ppm) (Deuteriochloroform)
3a	144	82	$C_4H_7N_3O_2S_2$	24.88 (24.69)	3.65 (3.76)	21.76 (21.68)	193 145	1690 (CO) 1100 (SO)	2.49 (s, 3H, SCH_3), 3.23 (s, 3H, NCH_3)
3b	75	88	$C_6H_{11}N_3O_2S_2$	32.58 (32.53)	5.01 (5.03)	19.00 (19.24)	221 173	1690 (CO) 1100 (SO)	1.48 (d, 6H, $(CH_3)_2C$-), 2.46 (s, 3H, SCH_3), 4.20-4.73 (m, 1H, $(CH_3)CH$)
3c	123	86	$C_9H_{15}N_3O_2S_2$	41.38 (41.43)	5.79 (5.82)	16.09 (16.32)	261 213	1695 (CO) 1100 (SO)	1.02-2.20 (m, 10H, c-C_6H_{10}), 2.48 (s, SCH_3), 3.88-4.40 (m, 1H, NCH)
3d	125	64	$C_9H_9N_3O_2S_2$	42.36 (42.40)	3.56 (3.53)	16.47 (16.43)	255 207	1695 (CO) 1100 (SO)	2.46 (s, 3H, SCH_3), 7.73 (s, 5H, aromatic)

[a] M^+ and M^+-SO. [b] In nujol.

Table II

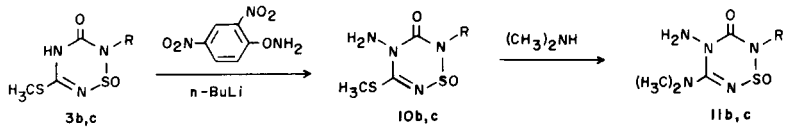
Analytical and Spectral Data of 4-Methylthiatriazines **4**, **5a-c** and **6a-c**

Compound	Mp °C	Yield (%)	Formula	Analysis % Calcd. (Found) C	H	N	MS [a]	IR, cm^{-1} [b]	PMR (δ ppm) (Deuteriochloroform)
4a	68	51 [c] 90 [d]	$C_5H_9N_3O_2S_2$	28.99 (28.93)	4.38 (4.34)	20.29 (20.26)	207 159	1680 (CO) 1100 (SO)	2.46 (s, 3H, SCH_3), 3.18 (s, 3H, 2-CH_3), 3.39 (s, 3H, 4-CH_3)
4b	58	58 [c] 95 [d]	$C_7H_{13}N_3O_2S_2$	35.74 (35.65)	5.57 (5.54)	17.87 (17.64)	235 187	1680 (CO) 1100 (SO)	1.45 (d, 6H, $(CH_3)_2C$), 2.49 (s, 3H, SCH_3), 3.40 (s, 3H, 4-CH_3), 4.18-4.64 (m, 1H, CH)
4c	oil	59 [c] 94 [d]	$C_{10}H_{17}N_3O_2S_2$	43.63 (43.54)	6.23 (6.15)	15.27 (15.25)	275 227	1690 (CO) 1120 (SO)	1.02-2.20 (m, 10H, c-C_6H_{10}), 2.49 (s, 3H, SCH_3), 3.37 (s, 3H 4-CH_3)
4d	oil	92 [d]	$C_{10}H_{11}N_3O_2S_2$	44.61 (44.67)	4.12 (4.15)	15.61 (15.46)	269 221	1690 (CO) 1120 (SO)	2.43 (s, 3H, SCH_3), 3.67 (s, 3H, 4-CH_3), 7.26 (s, 5H, aromatic)
5a	oil	86	$C_6H_{12}N_4O_2S$	35.29 (35.45)	5.92 (5.98)	27.44 (27.45)	204 156	1680 (CO) 1120 (SO)	2.96 (s, 6H, $(CH_3)_2N$), 3.18 (s, 3H, 2-CH_3), 3.38 (s, 3H, 4-CH_3)
5b	oil	85	$C_8H_{16}N_4O_2S$	41.37 (41.32)	6.94 (6.98)	24.13 (24.09)	232 184	1680 (CO) 1100 (SO)	1.43 (d, 6H, $(CH_3)_2C$), 2.97 (s, 6H, $(CH_3)_2N$), 3.41 (s, 3H, 4-CH_3)
5c	72	81	$C_{11}H_{20}N_4O_2S$	48.52 (48.50)	7.40 (7.67)	20.58 (20.54)	272 224	1680 (CO) 1100 (SO)	0.92-2.30 (m, 10H, c-C_6H_{10}), 2.95 (s, 6H, $(CH_3)_2N$), 3.39 (s, 3H, 4-CH_3)
6a	108 104-106 [e]	18	$C_6H_{12}N_4O_3S$	32.73 (32.54)	5.49 (5.42)	25.45 (25.65)	220 172	1685 (CO) 1300 (SO_2)	2.95 (s, 6H, $(CH_3)_2$), 3.34 (s, 3H, 4-CH_3), 3.44 (s, 3H, 2-CH_3)
6b	97 95 [e]	15	$C_8H_{16}N_4O_3S$	38.70 (38.65)	6.50 (6.45)	22.57 (22.48)	248 200	1680 (CO) 1300 (SO_2)	1.53 (d, 6H, $(CH_3)_2C$), 2.92 (s, 6H, $(CH_3)_2N$), 3.31 (s, 3H, 4-CH_3)
6c	133	10 89 [f]	$C_{11}H_{20}N_4O_3S$	45.82 (45.75)	6.99 (6.85)	19.44 (19.40)	288 240	1680 (CO 1300 (SO_2)	1.20-2.20 (m, 10H, c-C_6H_{10}), 3.01 (s, 6H, $(CH_3)_2N$), 3.29 (s, 3H, 4-CH_3)

[a] M^+ and M^+-SO in **4**, **5a-c**; M^+ and M^+-SO_2 in **6a-c**. [b] In nujol. [c] Procedure (A). [d] Procedure (B). [e] Lit [7]. [f] From **7c**.

either the N^4, N^6, or O^3 position, leading to **4**, **8** or **9**, respectively. The structure of **4** was elucidated on the basis of spectroscopic and chemical studies. The possibility of O^3-methylation to give 3-methoxy-5-methylthio-2*H*-1,2,4,6-thiatriazine-1-oxide **9** was ruled out because of infrared signals at 1680-1690 cm^{-1} presumably due to the carbonyl group. A distinction between structure **4** (N^4) and the alternative regioisomer **8** (N^6) by ^1H nmr and ultraviolet spectroscopic analyses was unsuccessful. Direct cyclization of 1-alkylcarbamoyl-1,3-dimethylisothiourea with thionyl chloride to give **8** under a variety of basic conditions resulted in failure and the starting material was almost recover-

Scheme III



b, R = i-C_3H_7, c, R = c-C_6H_{11}

Table III

Analytical and Spectral Data of 4-Aminothiatriazines **10b-c** and **11b-c**

Compound	Mp °C	Yield (%)	Formula	Analysis % Calcd. (Found) C	H	N	MS [a]	IR, cm^{-1} [b]	PMR (δ ppm) (Deuteriochloroform)
10 [b]	155	58	$C_6H_{12}N_4O_2S_2$	30.51 (30.56)	5.12 (5.34)	23.72 (23.67)	236	1685 (CO) 1120 (SO)	1.46 (s, 6H, $(CH_3)_2C$), 2.32 (s, 3H, SCH_3), 4.53 (br, s, 2H, N-NH_2)
10c	166	63	$C_9H_{16}N_4O_2S_2$	39.13 (39.09)	5.84 (5.93)	20.28 (20.19)	276	1685 (CO) 1120 (SO)	1.01-2.20 (m, 10H, c-C_6H_{10}), 2.32 (s, 3H, SCH_3), 4.43 (br, s, 2H, N-NH_2)
11b	114	89	$C_7H_{15}N_5O_2S$	36.05 (36.03)	6.48 (6.58)	30.03 (29.95)	233	1685 (CO) 1120 (SO)	1.46 (s, 6H, $(CH_3)_2C$), 3.13 (s, 6H, $(CH_3)_2N$), 4.53 (br s, 2H, N-NH_2)
11c	126	89	$C_{10}H_{19}N_5O_2S$	43.95 (43.87)	7.01 (7.09)	25.63 (25.65)	273	1685 (CO) 1120 (SO)	1.00-2.20 (m, 10H, c-C_6H_{10}), 3.09 (s, 6H, $(CH_3)_2N$), 4.58 (br s, 2H, N-NH_2)

[a] M^+. [b] In nujol.

ed. Treatment of **4** with excess dimethylamine in isopropyl alcohol at room temperature effected nucleophilic displacement affording the corresponding 6-dimethylamino-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides **5a-c** except **5d** in good yields. Under similar conditions, treatment of **4d** with dimethylamine resulted in the ring cleavage to give 1,1-dimethyl-3-phenylurea in a quantitative yield. Successive oxidation of **4a-c** with *m*-chloroperoxybenzoic acid in chloroform at room temperature gave **6a-c** in 10-18% yields, one, **6c** of which was identical, in all respects (melting point, ^1H nmr, infrared and mass spectra), with 2-cyclohexyl-5-dimethylamino-4-methyl-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1,1-dioxide prepared by the reaction of dimethylamine on 6-methylthio-2*H*-1,2,4,6-thiatriazin-3(2*H*)-one 1,1-dioxide (**7c**) [6]. We can now unequivocally state that methylation of **3** with either methyl iodide or diazomethane proceeds regioselectively to give the N^4-methylated 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxide (Scheme I).

On the basis of the above, the regioselective methylation of **3** at the N^4 nitrogen atom suggests that 3(4*H*)-one is a main tautomer. Further investigation is directed toward the amination of **3b-c** with the expectation of selective N^4 amination. Amination of **3b-c** with *O*-(2,4-dinitrophenyl)-hydroxylamine to give **10b-c** was accomplished in the presence of *n*-butyllithium in tetrahydrofuran at room temperature. Structural assignment of **10b-c** was based on the elemental analysis and on the spectral data. Infrared spectra showed strong absorption at 3200 and 3100 cm^{-1} (NH_2). The ^1H nmr spectra showed broad signal at δ 4.53-4.58 for the NH_2 group and a sharp singlet at δ 2.32 for the SCH} group. The SCH} group of **10b-c** is quite reactive and was smoothly displaced by dimethylamine at room temperature to provide **11b-c** (Scheme II). Attempt to oxidize the thiatriazin-3(4*H*)-one 1-oxide **11b-c** to the corresponding thiatriazin-3(4*H*)-one 1,1-dioxide, using *m*-chloroperoxybenzoic acid or trifluoroperoxyacetic acid under varied experimental conditions, led to complex mixtures.

In summary, this study represents the first example of the synthesis of 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides. Methylation and amination of 2*H*-1,2,4,6-thiatriazines afforded regioselectively N^4-methylated and -aminated thiatriazines, respectively. Some 2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-oxides and 1,1-dioxides have high potential herbicidal activities which will be later described elsewhere in detail.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Hitachi R-900 spectrometer operating at 90 MHz as an internal standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector; the ionizing

voltage was 70 eV. The ir spectra were recorded on a Hitachi 260-10 spectrometer.

5-Methylthio-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-Oxides **3**.

General Procedure.

To a solution of 10.0 mmoles of 1-carbamoyl-2-methylisothiourea **2** in 20 ml of pyridine was added dropwise 1.54 g (13.0 mmoles) of fresh thionyl chloride in 10 ml of chloroform at 5° under a nitrogen flow over 30 minutes. After the mixture was stirred at room temperature for 5 hours, the solution was poured into ice-water, and the product extracted with chloroform. The combined chloroform extracts were dried over magnesium sulfate, filtered and the solvent concentrated under reduced pressure. The crude oily product obtained by removal of chloroform *in vacuo* was subjected to silica gel column chromatography. Elution with benzene-ethyl acetate (4:1) gave purified compound **3** which on recrystallization from acetone-*n*-hexane afforded an analytical sample. The yields and physical properties of compounds **3a-d** are given in Table I.

4-Methyl-5-methylthio-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-Oxides **4**.

General Procedure (A).

A solution of 5.0 mmoles of 5-methylthio-2*H*-1,2,4,6-thiatriazines **3** in 30 ml of tetrahydrofuran was cooled in a dry ice-acetone bath under a nitrogen atmosphere, and then 2.6 ml (6.0 mmoles) of 2.3 *M* *n*-butyllithium in *n*-hexane was added over 10 minutes at a temperature below −5°. Thereafter a solution of 1.07 g (7.5 mmoles) of methyl iodide in 10 ml of tetrahydrofuran was added over 5 minutes at a temperature below −5°; the cooling bath was removed and stirring continued for 2 hours at room temperature. After the mixture was gently refluxed for 4 hours, the reaction was evaporated to dryness and extracted with chloroform. The combined chloroform extract was dried over magnesium sulfate, filtered and the solvent concentrated under reduced pressure. The crude product was chromatographed over silicic acid; *n*-hexane-acetone (5:1) eluted purified compound **4**, which on recrystallization from isopropyl alcohol-*n*-hexane yielded an analytical sample. The yields and physical properties of compounds **4a-c** are shown in Table I.

General Procedure (B).

To a solution of 5.0 mmoles of **3** in 30 ml of chloroform was slowly introduced diazomethane (15.0 mmoles) in 20 ml of diethyl ether below 10°. The solution was stirred overnight at room temperature. After removal of the solvent, the residual oil was recrystallized from isopropyl alcohol-*n*-hexane yielding an analytical sample. The yields and physical properties of compounds **4a-c** are given in Table I.

5-Dimthylamino-4-methyl-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-Oxides **5**.

General Procedure.

To a solution of 4.0 mmoles of 4-methyl-5-methylthio-2*H*-1,2,4,6-thiatriazines **4** in 20 ml of isopropyl alcohol was added 2 ml of isopropyl alcohol saturated with dimethylamine at 5°. After stirring for 1 hour at room temperature, the reaction mixture was concentrated under reduced pressure. The crude product was chromatographed over silicic acid; *n*-hexane-acetone (3:1) eluted purified compound **5** which on recrystallization from isopropyl alcohol-*n*-hexane gave an analytical sample. The yields and physical constants of compounds **5a-c** are shown in Table II.

5-Dimethylamino-4-methyl-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1,1-Dioxides **6**.

General Procedure from **5a-c**.

To a solution of 3.0 mmoles of 2*H*-1,2,4,6-thiatriazines **5a-c** in 30 ml of chloroform was added 6.0 mmoles (1.04 g) of *m*-chloroperoxybenzoic acid. After stirring overnight at room temperature, the mixture was evaporated to dryness and extracted with chloroform. The combined chloroform extracts were washed with aqueous sodium hydrogen carbonate and dried over magnesium sulphate. After removal of the solvent, the residue was chromatographed over silicic acid; *n*-hexane-acetone (3:1) eluted purified compound **6**, which on recrystallization from isopropyl alcohol-*n*-hexane gave an analytical sample. The yields and physical constants of compounds **6a-c** are shown in Table II.

2-Cyclohexyl-5-dimethylamino-4-methyl-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1,1-Dioxide **6c** From **7c**.

The reaction of 2-cyclohexyl-5-methylthio-2*H*-1,2,4,6-thiatriazin-3(4*H*)-1,2,4,6-thiatriazin-3(4*H*)-one 1,1-dioxide (**7c**) with dimethylamine was performed in the same method as described for the preparation of compounds **5** giving the corresponding 5-dimethylamino-2*H*-1,2,4,6-thiatriazine **6c**. Recrystallization from isopropyl alcohol-*n*-hexane gave an analytical sample. The yield and physical properties are shown in Table II.

4-Amino-5-methylthio-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-Oxides **10b,c**.

General Procedure.

To a solution of 5.0 mmoles of 2*H*-1,2,4,6-thiatriazines **3b-c** in 50 ml of tetrahydrofuran was cooled in a dry ice-acetone bath under a nitrogen atmosphere, and then 2.6 ml (6.0 mmoles) of 2.3 *M* *n*-butyllithium in *n*-hexane was added over 10 minutes at temperature below −5°. Thereafter a solution of 1.3 g (6.5 mmoles) of *O*-(2,4-dinitrophenyl)hydroxylamine in 20 ml of tetrahydrofuran was added over 15 minutes at temperature below 0°; the cooling bath was removed and stirring continued for 24 hours at room temperature. Addition of 10 ml of methanol was followed by removal of tetrahydrofuran under reduced pressure. The crude product was chromatographed over silicic acid; methanol-chloroform (1:80) eluted purified compound **10**, which on recrystallization from isopropyl alcohol an analytical sample. The yields and physical properties of compounds **10b-c** are shown in Table III.

4-Amino-5-dimethylamino-2*H*-1,2,4,6-thiatriazin-3(4*H*)-one 1-Oxides **11b,c**.

General Procedure.

The reaction of 4-amino-5-methylthio-2*H*-1,2,4,6-thiatriazine **10** with dimethylamine was performed by the same method as described for the preparation of compound **5** giving the corresponding 5-dimethylamino-2*H*-1,2,4,6-thiatriazine **11**. Recrystallization from isopropyl alcohol gave an analytical sample. The yields and physical constants of compounds **11b,c** are shown in Table III.

REFERENCES AND NOTES

[1] For the previous report in this series, see Y. Sanemitsu and Y. Nakayama, *Synthesis*, in press.

[2] Hexazinone **1** is 3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione, see D. A. Allison and T. D. Joyle, Proc. Br. Weed Control Conf., **12**, 279 (1974); K. Lin, U. S. Patent 3,902,887 (1975); *Chem. Abstr.*, **84**, 44170u (1976).

[3] A. Zeidler, A. Fisher and G. Weiss, U. S. Patent 3,708,277 (1973); Netherlands Patent 7,412,249 (1974).

[4] R. A. Wohl, U. S. Patent 4,209,624 (1980); *Chem. Abstr.*, **93**, 238867h (1980).

[5] S. D. Sinan, *J. Heterocyclic Chem.*, **16**, 895 (1979).

[6] One step preparation of 2-cyclohexyl-4-methyl-5-methylthio-2*H*-thiatriazin-3(4*H*)-one 1,1-dioxide (**7c**) was achieved through the direct cyclization of easily accessible 3-cyclohexylsulfamoyl-1,2-dimethylisothiourea with 1,1'-carbonyldiimidazole in 91% yield. See: Y. Nakayama and Y. Sanemitsu, *Synthesis*, in press.

[7] T. I. Kay, German Patent 2,508,832 (1975); *Chem. Abstr.*, **84**, 59585g (1976).