Preparation of 4-Substituted 3,5-Diaryloxy and 3,5-Diamino-1,2,4,6-Thiatriazine 1,1-Dioxides

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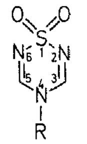
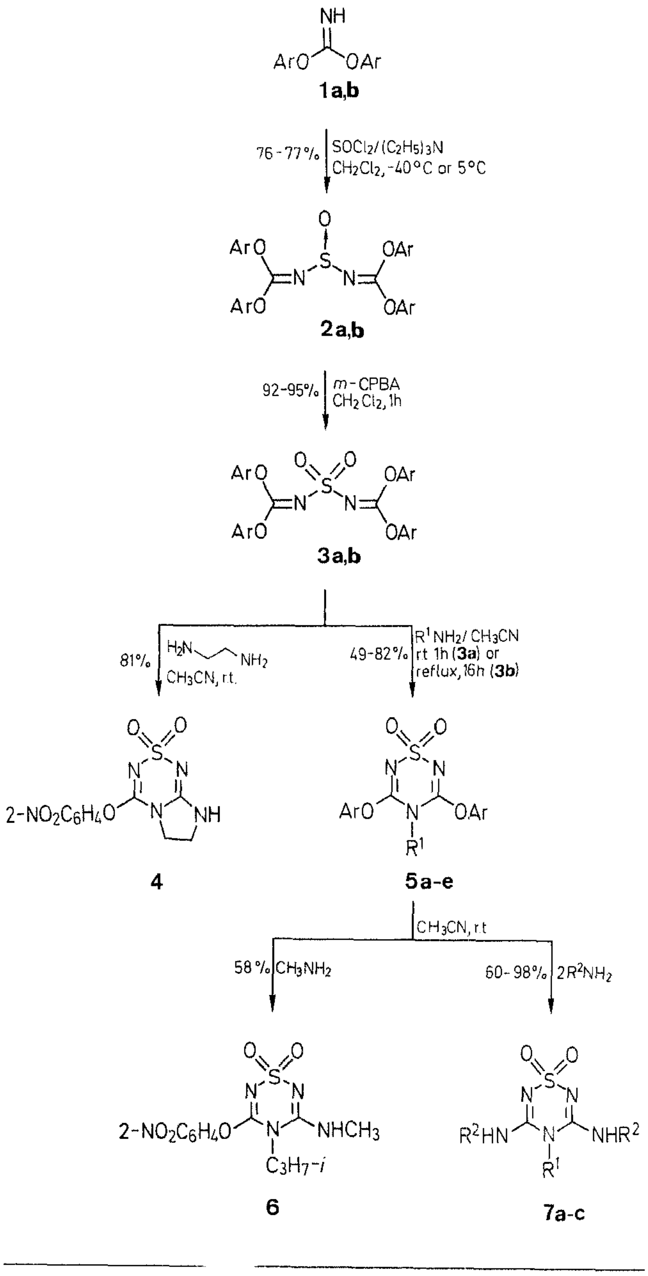
A new, technically simple synthesis of 4-substituted 1,2,4,6-thiatriazine-1,1-dioxides is presented which allows the easy preparation of a variety of new derivatives of this ring system.

Interest in the biological activity found in certain 1,2,4,6-thiatriazine-1,1-dioxide derivatives has led to the development of synthetic routes to the 2-alkyl,[1] 2,4-dialkyl,[2] and 4H[3] derivatives of this ring system. Only very recently have methods been reported[4] which make the 4-substituted isomers generally accessible.



4-Alkyl-1,2,4,6-Thiatriazine-1,1-dioxide



1-3	Ar
a	2-$NO_2C_6H_4$
b	4-$CH_3C_6H_4$

5	R^1	Ar
a	CH_3	4-$CH_3C_6H_4$
b	C_2H_5	4-$CH_3C_6H_4$
c	$HC{\equiv}C{-}CH_2$	4-$CH_3C_6H_4$
d	C_2H_5	2-$NO_2C_6H_4$
e	i-C_3H_7	2-$NO_2C_6H_4$

7	R^1	R^2
a	i-C_3H_7	CH_3
b	CH_3	H
c	C_2H_5	CH_3

We now wish to report a new simplified, efficient, and highly versatile synthesis of 4-substituted *thiatriazine derivatives* **4**, **5**, **6** and **7** which avoids the use of expensive and very reactive starting materials – chlorosulfonyl isocyanate or N-alkylaminosulfonylchlorides – and the application of special blocking groups and strong bases common to the other methods. In addition, the thiatriazines prepared by this route are usefully substituted by readily displaceable aryloxy groups at the 3 and/or 5 position of the ring, allowing further elaboration by, for example, nucleophilic displacement with amines. All of the intermediates and final products in this process are stable, crystalline compounds which either crystallize directly from the reaction solutions, or are obtained pure by simple recrystallization of the reaction mixture.

The starting *O*,*O*-diaryl carbonimidates **1** were readily prepared from cyanogen bromide and various phenols according to the procedure of Nef.[5] Diphenyl carbonimidates are in general unstable compounds, slowly forming the corresponding triazines on standing at room temperature. Substitution of the phenyl rings by strong electron withdrawing groups, however, increases stability such that the 2-nitro derivative **1a**[6] is a highly crystalline solid, stable for many months at room temperature.

In spite of their tendency to trimerize, freshly prepared *O*,*O*-diaryl carbonimidates could be reacted with thionyl chloride in the presence of triethylamine to give stable sulfoxide derivatives **2a** and **2b** in good yield. These were readily oxidized with *m*-chloroperoxybenzoic acid to the sulfamides **3a** and **3b** which are versatile intermediates for the preparation of a variety of 1,2,4,6-thiatriazine-1,1-dioxides.

Reaction of **3** with one equivalent of a primary amine gave the 4-substituted thiatriazines **5** by displacement of two aryloxy groups. Reaction with a diamine such as 1,2-diaminoethane afforded the bicyclic thiatriazine **4** directly. The reactivity of the sulfamide derivative **3** could be controlled by careful selection of the phenyl ring substituent. The 2-nitrophenyl compound **3a** was found to be particularly reactive, cyclizing at room temperature to thiatriazine **5**[7] even with fairly hindered amines such as isopropylamine. *t*-Butylamine failed to give cyclized product, however, and only the initial aduct formed by displacement of one aryloxy group was isolated from this reaction.

The remaining aryloxy groups of thiatriazines **4** and **5** could be sequentially displaced by further addition of amine or ammonia to give 3-amino- or 3,5-diaminothiatriazines such as **6** and **7**[4] (Table). A number of these diamino derivatives have been found to possess potent histamine H2-antagonist activity.[8]

Melting points were measured on a Kofler hot stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker 250 MHz instrument.

***N*,*N*'-Bis[di-(2-nitrophenoxy)methylene]sulfurous Diamide (2a):** Di(2-nitrophenyl) carbonimidate[6] (**1a**; 24.2 g, 80 mmol) is dissolved in dichloromethane (200 ml) containing triethylamine (8.8 g, 87 mmol) and the solution cooled to 5 °C in an ice bath. Thionyl chloride (4.76 g, 40 mmol) dissolved in dichloromethane (50 ml) is added dropwise to the stirred carbonimidate solution over a period of 30 min. Ice cooling is discontinued and the mixture is stirred for an additional 60 min before washing with water (3 × 100 ml), drying with magnesium sulfate, and evaporating *in vacuo* to obtain the title compound as a crystalline solid; yield: 20.2 g (77%); m.p. 179–180 °C (dichloromethane/toluene).

$C_{26}H_{16}N_6SO_{13}$ calc. C 47.85 H 2.47 N 12.88
(652.5) found 47.87 2.56 12.80

***N*,*N*'-Bis[di-(4-methylphenoxy)methylene]sulfurous Diamide (2b):** *p*-Cresol (43.2 g, 0.4 mol) and sodium hydroxide (18 g, 0.44 mol) are dissolved in water (800 ml), and cooled to 5 °C in an ice bath. The

Table. Compounds **4**, **5**, **6**, **7** Prepared

Product No.	Yield (%)	m.p. (°C)	Molecular Formula[a]	^{1}H-NMR (DMSO-d_6/TMS) δ (ppm)
4	81	331–333 (dec.)	$C_{10}H_9N_5SO_5$ (311.3)	3.67 (m, 2H); 4.24 (m, 2H); 7.63–8.28 (m, 4H); 8.98 (br s, 1H)
5a	82	291	$C_{17}H_{17}N_3SO_4$ (359.4)	2.34 (s, 6H); 3.35 (s, 3H); 7.25 (ABq, 8H)
5b	68	302–304	$C_{18}H_{19}N_3SO_4$ (373.4)	1.45 (t, 3H, J = 7.0 Hz); 2.34 (s, 6H); 4.22 (q, 2H, J = 7.0 Hz); 7.27 (ABq, 8H)
5c	65	280	$C_{19}H_{17}N_3SO_4$ (383.4)	2.35 (s, 6H); 3.31 (s, 1H); 5.05 (d, 2H, J = 2.2 Hz); 7.27 (ABq, 8H)
5d	75	318 (dec.)	$C_{16}H_{13}N_5SO_8$ (435.3)	1.50 (t, 3H, J = 7.0 Hz); 4.36 (q, 2H, J = 7.0 Hz); 7.67–8.34 (m, 8H)
5e	49	259–263 (dec.)	$C_{17}H_{15}N_5SO_8$ (499.4)	1.67 (d, 6H, J = 6.9 Hz); 5.37 (sept, 1H); 7.67–8.34 (m, 8H)
6	58	242	$C_{12}H_{15}N_5SO_5$ (341.3)	1.54 (d, 6H, J = 6.8 Hz); 2.80 (s, 3H); 4.61 (sept, 1H); 7.62–8.28 (m, 8H); 8.06 br s, 1H)
7a	60	270	$C_7H_{15}N_5SO_2$ (233.3)	1.42 (d, 6H, J = 7.1 Hz); 2.71 (s, 6H); 4.25 (sept, 1H); 6.81 (br s, 2H)
7b	98	325–327	$C_3H_7N_5SO_2$ (177.2)	3.19 (s, 3H); 7.44 (br s, 4H)
7c	78	340–342	$C_6H_{13}N_5SO_2$ (219.3)	1.12 (t, 3H, J = 7.0 Hz); 2.70 (s, 6H); 3.74 (q, 2H, J = 7.0 Hz); 7.42 (s, 2H)

[a] Microanalyses were in good agreement with calculated values: C ±0.1, H ±0.1, N ±0.1, S ±0.2 (Exceptions: **4**, N −0.48, S +0.39; **7a**, H −0.15, N −0.19).

mixture is stirred well, and cyanogen bromide (21.2 g, 0.20 mol) is added portionswise over a period of about 30 min. Ice cooling is discontinued, and the mixture stirred for a further 60 min before filtering off the imidocarbonate, which is washed thoroughly with water. The moist product is dissolved dichloromethane (300 ml) and dried with magnesium sulfate for 1 h at 20 °C. The filtered dichloromethane solution is then cooled to −40 °C and triethylamine (13.6 g, 130 mmol) is added. Thionyl chloride (7.32 g, 61 mmol) is then added to the stirred dichloromethane solution at a rate sufficient to maintain the reaction at −40 °C with continued cooling. When the addition is complete, the solution is allowed to come to ambient temperature and is washed with water (3 × 100 ml), dried with magnesium sulfate, and evaporated *in vacuo*; yield: 25 g (76%); m.p. 130–145 °C (ether). A sample recrystallized from ether is found to melt at 135 to 143 °C with decomposition.

$C_{30}H_{28}N_2SO_5$	Calc.	C 68.16	H 5.34	N 5.30
(528.6)	Found	68.10	5.38	5.26

N,*N*′-Bis[di-(2-nitrophenoxy)methylene]sulfuric Diamide (3a):

Compound **2a** (19.6 g, 30 mmol) is dissolved in dichloromethane (150 ml) and cooled to 5 °C in an ice bath. *m*-chloroperoxybenzoic acid (80%, 8 g, 40 mmol) dissolved in dichloromethane (100 ml) is added dropwise to the stirred sulfoxide solution. When addition is complete, the mixture is stirred for 60 min before filtering off the crystalline product, which is then washed thoroughly with ether and dried; yield: 16.1 g (80%); m.p. 200–203 °C.

A second crop of the title compound (2.9 g) is obtained by washing the dichloromethane mother liquors with aqueous sodium hydrogen carbonate solution (100 ml), drying with magnesium sulfate, and evaporating *in vacuo*. A sample recrystallized from chloroform/ether melts sharply at 203 °C; total yield: 19.0 g (95%).

$C_{26}H_{16}N_6SO_{14}$	calc.	C 46.71	H 2.41	N 12.47
(668.5)	found	46.63	2.50	12.59

N,*N*′-Bis[di-(4-methylphenoxy)methylene]sulfuric Diamide (3b):

Compound **2b** (21.1 g, 40 mmol) is dissolved in dichloromethane (100 ml) and cooled to 5 °C in an ice bath. *m*-chloroperoxybenzoic acid (80%, 10 g, 50 mmol) dissolved in dichloromethane (100 ml) is added dropwise to the stirred sulfoxide solution. When the addition is complete, the mixture is stirred for further 60 min and then washed with a 5% aqueous sodium hydrogen carbonate solution (2 × 50 ml), dried with magnesium sulfate, and evaporated *in vacuo*. The residual crystalline solid is recrystallized from dichloromethane/ether to give **3b**; yield: 19.9 g (92%); m.p. 188–190 °C. One more recrystallization gives a sample having a m.p. of 193–194 °C.

$C_{30}H_{28}N_2SO_6$	calc.	C 66.16	H 5.18	N 5.14
(544.6)	found	66.07	5.22	5.12

4-(2-Nitrophenoxy)7,8-dihydro-6*H*-imidazo[2,1-*c*][1,2,4,6]thiatriazine 2,2-Dioxide (4):

Compound **3a** (1.34 g, 2 mmol) is suspended in acetonitrile (25 ml) and 1,2-diaminoethane (120 mg, 2 mmol) is added to the stirred suspension at 20 °C. After stirring at this temperature for 16 h, the resulting fine crystalline solid is collected by filtration, washed thoroughly with ether, and dried *in vacuo*; yield: 506 mg (81%); m.p. 331–333 °C (dec.).

$C_{10}H_9N_5SO_5$	calc.	C 38.59	H 2.91	N 22.50	S 10.30
(311.3)	found	38.61	2.98	22.02	10.69

Thiatriazines 5a, b, c; General Procedure:

Compound **3b** (1.088 g, 2 mmol) is suspended in acetonitrile (30 ml). This suspension is stirred well, and to it is added, at 20 °C, the appropriate amine (2 mmol). The clear solution which forms immediately after addition of the amine is heated to reflux for 16 h, then evaporated *in vacuo* to yield the product as a crystalline solid, which is recrystallized from acetonitrile/ether or ethanol (Table).

Thiatriazines 5d, e; General Procedure:

Compound **3a** (2.68 g, 4 mmol) is suspended in acetonitrile (100 ml), and the amine (4 mmol) is added dropwise to the stirred suspension at 20 °C. The resulting clear orange solution is stirred for 1 h at 20 °C and then concentrated to a volume of 20 ml *in vacuo*. The crystalline product is filtered off and recrystallized from acetonitrile (Table).

Thiatriazines 6, 7a, b, c; General Procedure:

Compound **5e** (450 mg, 1 mmol) is suspended in acetonitrile (20 ml) and methylamine (32 mg, 1 mmol) in acetonitrile (1 ml) is added at 20 °C. The mixture is stirred at 20 °C for 18 h and the solvent evaporated *in vacuo* to yield a crystalline residue which is chromatographed on silica gel using chloroform/acetonitrile (1:1) as eluent. Pure **6** is obtained by recrystallization from ethanol.

Use of thiatriazines **5a, b, d,** or **e** together with an excess of amine or ammonia in the above procedure, affords the corresponding 3,5-diaminothiatriazine **7a, b,** or **c**. These are obtained directly by evaporating the solvent and excess amine *in vacuo* and recrystallizing the residue from ethanol.

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(7) All of the compounds **2–7** presented in this paper are new except for **5a** and **7b** which we have previously prepared using different methodology (see ref. 4).

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