Cycloaddition in Synthesis of Sulfonamide Derivatives. III. Convenient Synthesis of 3-Alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-Dioxides

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Synthesis of 3-alkylthio-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxides was conveniently achieved by [2+2] cycloaddition reaction of *S*-alkyl *N*-methyl-*N*-phenyldithiocarbamates with chlorosulfonyl isocyanate with subsequent loss of carbonyl sulfide, followed by cyclization of the resulting chlorosulfonyl isothioureas under Friedel–Crafts conditions.

Keywords [2+2] cycloaddition; dithiocarbamate; chlorosulfonyl isocyanate; Friedel–Crafts cyclization; 3-alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxide

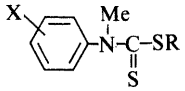
Some 3-alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxides have been reported to show antimicrobial activity.[1] They have been prepared by allowing 2-aminobenzenesulfonamides to react with thiourea[1a] or thiophosgene[2] followed by alkylation. These synthetic methods, however, have various disadvantages, *e.g.*, isomer formation, side reaction and the usage of hazardous reagents. To solve these problems and to obtain new derivatives, we developed a new synthetic method for 3-alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxides.

We recently reported[3] the synthesis of *N*-(*C*-aminoalkylthiomethylene)benzenesulfonamides (**4**) by use of a novel [2+2] cycloaddition reaction of sulfonyl isocyanate with dithiocarbamates. When the C–SO_2 bond of the benzothiadiazine dioxides is cleaved, the chemical structures correspond to those of **4**. These circumstances led us to develop a new synthetic method for benzothiadiazine dioxides.

In this paper, we report a simple, one-pot synthesis of 3-alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxide using a [2+2] cycloaddition reaction of *S*-alkyl *N*-methyl-*N*-phenyldithiocarbamates with chlorosulfonyl isocyanate with subsequent loss of carbonyl sulfide, followed by cyclization of the resulting chlorosulfonyl isothioureas with Lewis acid.

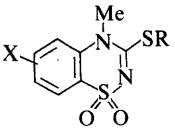
The starting dithiocarbamates (**1a—g**) were easily prepared from the corresponding *N*-methylanilines and alkyl

TABLE I. *S*-Alkyl *N*-Methyl-*N*-phenyldithiocarbamates (**1a—g**)



	R	X	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
1a	Me	H	82—83	$C_9H_{11}NS_2$	54.78 (54.78)	5.62 (5.66)	7.10 (7.10)
1b	Et	H	99—100	$C_{10}H_{13}NS_2$	56.83 (56.78)	6.20 (6.04)	6.63 (6.57)
1c	*n*-Pr	H	52—54	$C_{11}H_{15}NS_2$	58.62 (58.71)	6.71 (6.71)	6.21 (6.24)
1d	Me	4-Me	80—81	$C_{10}H_{13}NS_2$	56.84 (56.85)	6.20 (6.39)	6.63 (6.65)
1e	Me	4-OMe	93—94	$C_{10}H_{13}NOS_2$	52.83 (52.55)	5.76 (5.68)	6.16 (6.07)
1f	Et	4-OMe	77—78	$C_{11}H_{15}NOS_2$	54.74 (54.44)	6.26 (6.18)	5.80 (5.88)
1g	Me	2-Me	Oil	$C_{10}H_{13}NS_2$	56.84 (56.82)	6.20 (6.23)	6.63 (6.79)

TABLE II. 3-Alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-Dioxides (**2a—g**)



	R	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	Me	H	27	215—217	$C_9H_{10}N_2O_2S_2$	44.61 (44.54)	4.16 (4.10)	11.56 (11.62)
2b	Et	H	17	122—123	$C_{10}H_{12}N_2O_2S_2$	46.85 (46.89)	4.72 (4.74)	10.93 (10.83)
2c	*n*-Pr	H	12	127—128	$C_{11}H_{14}N_2O_2S_2$	48.87 (48.81)	5.22 (5.19)	10.36 (10.20)
2d	Me	7-Me	24	183—184	$C_{10}H_{12}N_2O_2S_2$	46.85 (46.81)	4.72 (4.60)	10.93 (10.88)
2e	Me	7-OMe	21	222—223	$C_{10}H_{12}N_2O_3S_2$	44.10 (44.04)	4.44 (4.38)	10.29 (10.31)
2f	Et	7-OMe	14	161—162	$C_{10}H_{14}N_2O_3S_2$	46.14 (46.22)	4.93 (4.92)	9.78 (9.83)
2g	Me	5-Me	5	178—181	$C_{10}H_{12}N_2O_2S_2$	46.85 (46.83)	4.72 (4.73)	10.93 (10.64)

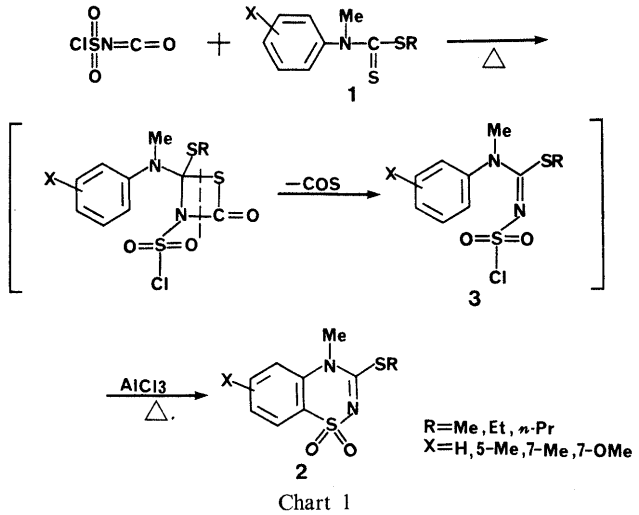


Chart 1

TABLE III. Spectral Data for *S*-Alkyl *N*-Methyl-*N*-phenyl Dithiocarbamates (**1a**—**g**)

	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (–N=C=S)	^{1}H-NMR ($CDCl_3$) δ (ppm)
1a	1490	2.55 (3H, s), 3.80 (3H, s), 7.12—7.78 (5H, m)
1b	1490	1.25 (3H, t, J=7 Hz), 3.20 (2H, q, J=7 Hz), 3.78 (3H, s), 7.00—7.62 (5H, m)
1c	1495	0.93 (3H, t, J=7 Hz), 1.23—2.00 (2H, m), 3.17 (2H, t, J=7 Hz), 3.75 (3H, s), 6.95—7.60 (5H, m)
1d	1505	2.42 (3H, s), 2.55 (3H, s), 3.78 (3H, s), 7.17 (2H, d, J=8 Hz), 7.28 (2H, d, J=8 Hz)
1e	1505	2.52 (3H, s), 3.72 (3H, s), 3.82 (3H, s), 6.88 (2H, d, J=9 Hz), 7.08 (2H, d, J=9 Hz)
1f	1505	1.27 (3H, t, J=7 Hz), 3.18 (2H, q, J=7 Hz), 3.75 (3H, s), 3.85 (3H, s), 6.95 (2H, d, J=9 Hz), 7.17 (2H, d, J=9 Hz)
1g	1490	2.20 (3H, s), 2.52 (3H, s), 3.68 (3H, s), 6.90—7.57 (4H, m)

TABLE IV. Spectral Data for 3-Alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-Dioxides (**2a**—**g**)

	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
2a	1095, 1165, 1310, 1350, 1465	2.63 (3H, s), 3.68 (3H, s), 7.17—7.92 (3H, m), 8.03 (1H, dd, J=2, 8 Hz)
2b	1100, 1165, 1315, 1350, 1465	1.42 (3H, t, J=7 Hz), 3.22 (2H, q, J=7 Hz), 3.63 (3H, s), 7.08—7.89 (3H, m), 7.93 (1H, dd, J=2, 7 Hz)
2c	1100, 1170, 1315, 1350, 1470	1.06 (3H, t, J=7 Hz), 1.50—2.17 (2H, m), 3.22 (2H, t, J=7 Hz), 3.67 (3H, s), 7.12—7.83 (3H, m), 7.97 (1H, dd, J=2, 7 Hz)
2d	1095, 1240, 1295, 1360, 1505	2.43 (3H, s), 2.62 (3H, s), 3.67 (3H, s), 7.06—7.67 (2H, m), 7.83 (1H, br s)
2e	1095, 1160, 1310, 1485, 1520	2.62 (3H, s), 3.65 (3H, s), 3.87 (3H, s), 7.10—7.25 (2H, m), 7.37—7.50 (1H, m)
2f	1095, 1165, 1310, 1485, 1510	1.40 (3H, t, J=7 Hz), 3.20 (2H, q, J=7 Hz), 3.60 (3H, s), 3.83 (3H, s), 7.03—7.17 (2H, m), 7.30—7.43 (1H, m)
2g	1095, 1140, 1310, 1330, 1505	2.52 (3H, s), 2.62 (3H, s), 3.70 (3H, s), 7.12—7.50 (2H, m), 7.67—7.88 (1H, m)

halides by a previously reported method.[4] The structures were confirmed by elemental analysis and spectral data, such as infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR). The results are summarized in Tables I and III.

In order to extend the applicability of our novel reaction,[4] these dithiocarbamates (**1a**—**g**) were made to react with chlorosulfonyl isocyanate and cyclization of the intermediates was tried to obtain the desired derivatives. For example, chlorosulfonyl isocyanate was added in portions, to an ice-cooled solution of **1a** in dichloroethane. The mixture was stirred at 50—60 °C for 2 h and the expected *N*-chlorosulfonyl isothiourea (**3**) was obtained *in situ*. This *N*-chlorosulfonyl isothiourea (**3**), which seems to be rather unstable during handling and storage,[5] underwent Friedel–Crafts cyclization to the desired bicyclic compound (**2a**) in the presence of anhydrous aluminum chloride. Elemental analysis of **2a** for carbon, hydrogen and nitrogen gave values that were in reasonably good agreement with the calculated values for $C_9H_{10}N_2O_2S_2$. The IR spectrum of **2a** showed characteristic peaks at 1165 and 1350 cm^{-1} attributable to the $-SO_2-$ group. The ^{1}H-NMR spectrum of **2a** indicated the presence of methylthio protons δ 2.63 (3H, s), *N*-methyl protons 3.68 (3H, s) and aromatic protons 7.17—7.92 (3H, m), 8.03 (1H, dd, J=8, 2 Hz). On the basis of these data, the structure of **2a** was established as 3-methylthio-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide. Friedel–Crafts cyclization using nitromethane as a solvent gave similar results. A plausible reaction sequence for the present reaction is shown in Chart 1. As described above, 4*H*-1,2,4-benzothiadiazine 1,1-dioxide derivatives were also obtained. The results are summarized in Table II.

In summary, from the viewpoints of simple procedure and the commercial availability of chlorosulfonyl isocyanate, this new method is very convenient for the preparation of 3-alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxides.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi 260-10 spectrometer. ^{1}H-NMR were determined on a JEOL JNM-PMX 60 instrument. Chemical shifts were reported as δ values downfield relative to internal tetramethylsilane. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad and dd=double doublet.

General Procedure for Preparation of Dithiocarbamates (1a—g) NaOH (42 mmol) and CS_2 (42 mmol) were added to a solution of the *N*-methyl amine (21 mmol) in EtOH (20 ml). The resulting suspension was stirred for 1 d at room temperature, then an alkyl halide (25 mmol) was added dropwise and the mixture was further stirred for 1 d. After removal of the solvent, the residue was poured into water and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography with hexane–AcOEt (95:5).

General Procedure for Preparation of 3-Alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (2a—g) Chlorosulfonyl isocyanate (2.9 mmol) was added dropwise to an ice-cooled solution of dithiocarbamate (2.4 mmol) in CH_2ClCH_2Cl (5 ml). The mixture was stirred at 50—60 °C for 2 h. After removal of the solvent, the residue was dissolved in nitromethane (5 ml) and the solution was cooled to 5 °C, then aluminum chloride (2.6 mmol) was added all at once. The reaction mixture was placed in a oil bath at 100 °C for 30 min, cooled, poured into water and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography with hexane–AcOEt–CH_2Cl_2 (4:2:3).

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