[Chem. Pharm. Bull. 36(12)4755—4759(1988)]

Cycloaddition in Synthesis of Sulfonamide Derivatives. I. A New Method for Preparation of *N*-(*C*-Amino-alkylthiomethylene)benzenesulfonamide

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(Received May 23, 1988)

A novel [2+2] cycloaddition reaction of benzenesulfonyl isocyanate is reported which can serve as a new, general method for the preparation of *N*-(*C*-amino-alkylthiomethylene)benzenesulfonamide. Benzenesulfonyl isocyanates underwent a [2+2] cycloaddition reaction with dithiocarbamates, which were obtained by treating amines with carbon disulfide and potassium carbonate, to give *N*-(*C*-amino-alkylthiomethylene)benzenesulfonamides in good yields.

Keywords——benzenesulfonyl isocyanate; [2+2] cycloaddition; dithiocarbamate; *N*-(*C*-amino-alkylthiomethylene)benzenesulfonamide; X-ray structure analysis

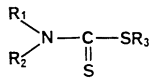
In the past decade, organic chemists have made considerable efforts to synthesize sulfonamide derivatives, because they are of interest pharmacologically.[1] However, there have been few studies on the synthesis of *N*-(*C*-amino-alkylthiomethylene)benzenesulfonamide derivatives, in which we are interested[2]: Kuwayama and Kataoka reported the synthesis of *N*-[(methylthio)aminomethylene]sulfanilamide from *N*-bis(methylthio)methylenebenzenesulfonamide, while Neidlein and Haussmann reported the preparation of *N*-[*C*-(*N*-methylanilino)methylthiomethylene]benzenesulfonamide in three steps starting from benzenesulfonamide. In trying to obtain our target compounds, we found the former method to be of limited utility, mainly due to the low nucleophilicity of the required *N*-substituted anilines. Also, the latter method was complicated and the overall yield was unsatisfactory.

In searching for a new, more effective and convenient synthesis of our target compounds, we turned our attention to a recently discovered novel reaction of benzenesulfonyl isocyanate with dithiocarbamate which led to sulfonylimine. Here we report our new method for the synthesis of the title compounds; it is easy to perform and enables us to synthesize novel benzenesulfonamide derivatives.

Initially, the starting dithiocarbamates (**1a**—**f**) were prepared from the corresponding amines and alkyl halides by a previously reported method.[3] 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 Table I.

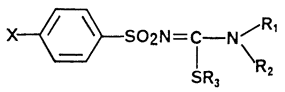
Next, reactions of these dithiocarbamates (**1a**—**f**) with benzenesulfonyl isocyanates were carried out. For example, **1a** was treated with *p*-toluenesulfonyl isocyanate in toluene under reflux for 6 h and gave **2a** as colorless crystals in good yield. The ^{1}H-NMR spectra of **2a** indicated the presence of methylthio protons (δ: 2.27, 3H, s), *N*-methyl protons (δ: 3.48, 3H, s) and aromatic protons (δ: 6.95—8.15, 10H, m). The IR spectra of **2a** revealed a C=N bond at 1545 cm^{-1}. Analysis of **2a** for carbon, hydrogen and nitrogen gave values that were in reasonably good agreement with calculated values for $C_{15}H_{16}N_2O_2S_2$. On the basis of these

TABLE I. Dithiocarbamates (**1a**—**f**)



	R_1	R_2	R_3	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
1a	Ph	Me	Me	82—83	$C_9H_{11}NS_2$	54.78	5.62	7.10
						(54.78	5.66	7.10)
1b	Ph	Me	*n*-Pr	52—54	$C_{11}H_{15}NS_2$	58.62	6.71	6.21
						(58.71	6.71	6.24)
1c	Ph	Me	iso-Pr	72—73	$C_{11}H_{15}NS_2$	58.62	6.71	6.21
						(58.58	6.74	6.28)
1d	Indolinyl		Me	87—88	$C_{10}H_{11}NS_2$	57.38	5.30	6.69
						(57.33	5.35	6.76)
1e	Ph	Me	iso-Pent	39—40	$C_{13}H_{19}NS_2$	61.61	7.56	5.53
						(61.60	7.58	5.62)
1f	Ph	Me	*tert*-Bu	108—109	$C_{12}H_{17}NS_2$	60.21	7.16	5.85
						(60.27	7.09	5.84)

TABLE II. *N*-(*C*-Amino-alkylthiomethylene)benzenesulfonamide (**2a**—**k**)



	R^1	R^2	R^3	X	*E* or *Z*	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
2a	Ph	Me	Me	H	*Z*	95	Oil	$C_{15}H_{16}N_2O_2S_2$	56.22	5.03	8.74
									(55.98	5.09	8.95)
2b	Ph	Me	Me	Cl	*Z*	84	Oil	$C_{15}H_{15}ClN_2O_2S_2$	50.77	4.26	7.89
									(50.69	4.27	7.95)
2c	Ph	Me	*n*-Pr	Me	*Z*	90	105—107	$C_{18}H_{22}N_2O_2S_2$	59.64	6.12	7.73
									(59.50	6.23	7.77)
2d	Indolyl		Me	H	—	98	131—134	$C_{16}H_{16}N_2O_2S_2$	57.81	4.85	8.43
									(57.51	4.71	8.37)
2e	Indolyl		Me	Cl	—	82	161—164	$C_{16}H_{15}ClN_2O_2S_2$	52.38	4.12	7.64
									(52.40	4.19	7.61)
2f	Ph	Me	*n*-Pr	Cl	*Z*	96	109—112	$C_{17}H_{19}ClN_2O_2S_2$	53.32	5.00	7.32
									(53.30	5.05	7.26)
2g	Ph	Me	iso-Pr	H	*Z*	93	Oil	$C_{17}H_{20}N_2O_2S_2$	58.59	5.78	8.04
									(58.46	5.80	7.97)
2h	Ph	Me	iso-Pr	Me	*Z*	89	83—84	$C_{18}H_{22}N_2O_2S_2$	59.64	6.12	7.73
									(59.51	6.18	7.72)
2i	Ph	Me	iso-Pr	Cl	*Z*	95	Oil	$C_{17}H_{19}ClN_2O_2S_2$	53.32	5.00	7.32
									(53.32	5.07	7.32)
2j	Ph	Me	iso-Pent	Me	*Z*	95	58—59	$C_{20}H_{26}N_2O_2S_2$	61.51	6.71	7.17
									(61.60	6.67	7.24)
2k	Ph	Me	*tert*-Bu	Me	*E*	46	124—125	$C_{19}H_{24}N_2O_2S_2$	60.61	6.42	7.44
									(60.59	6.38	7.41)

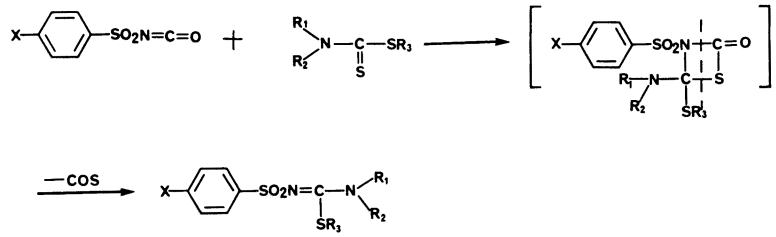


Chart 1

TABLE III. Spectral Data for Dithiocarbamates (**1a**—**f**)

	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (ν-N=C=S)	^{1}H-NMR ($CDCl_3$) δ (ppm)
1a	1490	2.55 (3H, s), 3.80 (3H, s), 6.88—7.88 (5H, m)
1b	1495	0.92 (3H, t, J=9 Hz), 1.18—2.02 (2H, m), 3.15 (2H, t, J=8 Hz), 3.75 (3H, s), 6.75—7.62 (5H, m)
1c	1495	1.33 (6H, d, J=7 Hz), 3.73 (3H, s), 4.05 (1H, sept, J=7 Hz), 7.07—7.57 (5H, m)
1d	1490	2.67 (3H, s), 3.13 (2H, t, J=8 Hz), 4.42 (2H, t, J=8 Hz), 6.87—7.43 (3H, m), 8.77—9.10 (1H, m)
1e	1495	0.92 (6H, d, J=6 Hz), 2.23—2.95 (3H, m), 3.06—3.32 (2H, m), 3.75 (3H, s), 6.92—7.78 (5H, m)
1f	1495	1.15 (9H, s), 2.40 (3H, s), 3.74 (3H, s), 7.10—8.05 (9H, m)

TABLE IV. Spectral Data for *N*-(*C*-Amino-alkylmercaptomethylene)benzenesulfonamides (**2a**—**k**)

	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
2a	1090, 1145, 1505, 1545	2.27 (3H, s), 3.48 (3H, s), 6.95—8.15 (10H, m)
2b	1090, 1245, 1505, 1545	2.26 (3H, s), 3.49 (3H, s), 7.02—8.09 (9H, m)
2c	1085, 1140, 1495, 1540	0.73 (3H, t, J=7 Hz), 0.97—1.80 (2H, m), 2.42 (3H, s), 2.70 (2H, t, J=8 Hz), 3.57 (3H, s), 6.95—8.27 (9H, m)
2d	1150, 1460, 1480, 1500	2.72 (3H, s), 3.07 (2H, t, J=8 Hz), 4.25 (2H, t, J=8 Hz), 6.67—8.13 (9H, m)
2e	1150, 1460, 1475, 1500	2.70 (3H, s), 3.10 (2H, t, J=8 Hz), 4.28 (2H, t, J=8 Hz), 6.80—8.03 (8H, m)
2f	1090, 1150, 1500, 1545	0.75 (3H, t, J=7 Hz), 1.08—1.75 (2H, m), 2.70 (2H, t, J=8 Hz), 3.50 (3H, s), 7.00—8.00 (9H, m)
2g	1085, 1145, 1495	1.03 (6H, d, J=7 Hz), 3.37 (1H, sept, J=7 Hz), 3.53 (3H, s), 7.00—8.13 (10H, m)
2h	1090, 1145, 1495	1.10 (6H, d, J=7 Hz), 2.42 (3H, s), 3.37 (1H, sept, J=7 Hz), 3.53 (3H, s), 7.10—8.03 (9H, m)
2i	1085, 1145, 1490	1.12 (6H, d, J=7 Hz), 3.40 (1H, sept, J=7 Hz), 3.53 (3H, s), 7.10—8.07 (9H, m)
2j	1090, 1150, 1495, 1545	0.72 (6H, d, J=6 Hz), 0.95—1.58 (3H, m), 2.42 (3H, s), 2.58—2.92 (2H, m), 3.57 (3H, s), 7.08—8.12 (9H, m)
2k	1085, 1145, 1530	1.15 (9H, s), 2.40 (3H, s), 3.74 (3H, s), 7.10—8.05 (9H, m)

Sept = septet.

data, the structure **2a** was established to be *N*-[*C*-(*N*-methylanilino)methylmercaptomethylene]benzenesulfonamide. In the same way, **2b**—**k** were obtained from the corresponding dithiocarbamates and sulfonyl isocyanates in good yields (Table II). These results suggest that the reaction proceeded *via* intermolecular [2+2]cycloaddition of the C=N group of the sulfonyl isocyanate to the C=S group of the dithiocarbamate with subsequent loss of carbonyl sulfide.

Numerous studies have been done on the [2+2] cycloaddition reaction of sulfonyl

2f 2k

Fig. 1. Molecular Structures of **2f** and **2k**

isocyanates,[4] but there has been no previous report of a [2+2] cycloaddition reaction of sulfonyl isocyanate with dithiocarbamate.

The configurations of the compounds obtained were assigned from their ^{1}H-NMR spectra. The chemical shifts of the *N*-methyl protons could be conveniently divided into two groups: those with upfield resonance, **2a**—**c**, **2f**—**j** (3.48—3.57 ppm) and that with lowfield resonance, **2k** (3.74 ppm). In the ^{1}H-NMR spectra of their oxime tosylates, Bull *et al.* found that the methine proton of the cyclopropyl group resonated at a lower field when the cyclopropyl group was *cis* to the sulfonyl group than when it was *trans* to the sulfonyl group.[5] By analogy, the *E* configuration was assigned to **2k** which had the signal due to the *N*-methyl group at lower field, and *Z* configurations were assigned to the others (**2a**—**c**, **2f**—**j**). As configurational assignments are based on relative *N*-methyl chemical shifts, **2d** and **2e** could not be assigned configurations. In order to check the ^{1}H-NMR configurational assignment, X-ray structure analyses of **2f** and **2k** were undertaken. The results supported our configurational assignments (Fig. 1).[6]

In conclusion, our new method of [2+2] cycloaddition of benzenesulfonyl isocyanate provides an alternative to the known methods for the preparation of *N*-(*C*-aminoalkylthiomethylene)benzenesulfonamide in terms of simplicity, generality and yield.

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 spectra were determined on a JEOL JNM-PMX60 instrument. Chemical shifts are reported as δ values downfield relative to internal tetramethylsilane. The following abbreviations are used: s=singlet, d=doublet, t=triplet, sept=septet and m=multiplet. Toluene was freshly distilled from CaH_2.

General Procedure for Preparation of Dithiocarbamate (1a—f)——K_2CO_3 (34 mmol) and CS_2 (2.6 ml) were added to a solution of the *N*-methyl amine (30 mmol) in EtOH (20 ml). The resulting suspension was stirred for 4 h at room temperature, then an alkyl halide (30 mmol) was added dropwise and the mixture was further stirred for 20 h. 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–CH_2Cl_2 (1 : 1).

General Procedure for Preparation of *N*-(*C*-Amino-alkylthiomethylene)benzenesulfonamide (2a—k)——A mixture of dithiocarbamate (4.3 mmol) and sulfonyl isocyanate (5.2 mmol) in toluene (11 ml) was refluxed for 6 h. The mixture was diluted with CH_2Cl_2 (100 ml), washed with water (50 ml), and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography with hexane–AcOEt (2 : 1).

Acknowledgement We wish to express our thanks to Dr. Yoshiyuki Hayashi, Director of the Aburahi Laboratories of Shionogi & Co., Ltd., for his encouragement and permission to publish this work.

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