Cycloaddition in Synthesis of Sulfonamide Derivatives. II.[1] Synthesis of *N*-Arylsulfonylethoxalamides by Cycloaddition of Arylsulfonyl Isocyanates to Ethyl Oxamates

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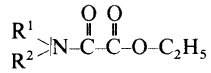
A new class of sulfonamides, N^2-arylsulfonyl-N^1,N^1-disubstituted ethoxalamidines, was synthesized by reaction of arylsulfonyl isocyanates with *N*,*N*-disubstituted ethyl oxamates. It was suggested that the reaction might proceed through [2+2] cycloaddition of the isocyanates to an amide carbonyl moiety with high selectivity.

Keywords sulfonamide; ethoxalamide; sulfonyl isocyanate; ethyl oxamate; [2+2] cycloaddition

Sulfonyl isocyanates have been shown to undergo a [2+2] cycloaddition reaction with carbon-heteroatom double bonds to give sulfonamide derivatives.[2] In an earlier study we reported a facile [2+2] cycloaddition reaction of arylsulfonyl isocyanate (ASI) with *N*,*N*-disubstituted dithiocarbamates leading to the formation of *N*-[alkylthio(anilino)methylene]-arylsulfonamides in good yields.[1] In order to introduce a new functional group, such as a carbonyl group into the amidine moiety, we have attempted a cycloaddition reaction of ASI with a compound having two different carbonyl groups. The work in this paper deals with a new, efficient reaction to form N^2-arylsulfonyl ethoxalamidines (**2a**—**j**) through a [2+2] cycloaddition reaction of ASI with *N*,*N*-disubstituted ethyl oxamates (**1**).

The starting materials **1** were prepared from the corresponding amines and ethyl oxalyl chloride. The results are summarized in Tables I and II.

TABLE I. *N*,*N*-Disubstituted Ethyl Oxamates (**1a**—**g**)



	R^1	R^2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
1a[a]	Phenyl	Methyl	Oil	100	$C_{11}H_{13}NO_3$			
1b	4-Chlorophenyl	Methyl	Oil	100	$C_{11}H_{12}ClNO_3$	54.67	5.00	5.80
						(54.34	5.12	5.97)
1c[b]	2-Chlorophenyl	Methyl	Oil	95	$C_{11}H_{12}ClNO_3$			
1d[a]	4-Methoxyphenyl	Methyl	Oil	95	$C_{12}H_{15}NO_4$			
1e	2-Methylphenyl	Methyl	Oil	93	$C_{12}H_{15}NO_3$	65.15	6.83	6.33
						(65.33	6.83	6.48)
1f	3-Pyridyl	Methyl	Oil	74	$C_{10}H_{12}N_2O_3$	57.68	5.81	13.45
						(57.48	5.97	13.37)
1g	Phenyl	Phenyl	76—77	72	$C_{16}H_{15}NO_3$	71.36	5.61	5.20
						(71.44	5.72	5.29)

a) L. Baiocchi, *Ann. Chim.*, **57**, 492 (1967). *b*) B. J. James, P. K. Peter, R. C. Francis, L. D. Kenneth and B. M. Joseph, Ger. Offen. 2819878 (1978) [*Chem. Abstr.*, **90**, 134010*v* (1979)].

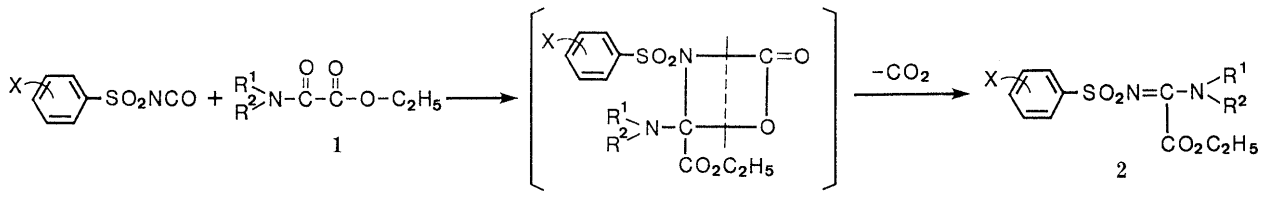


Chart 1

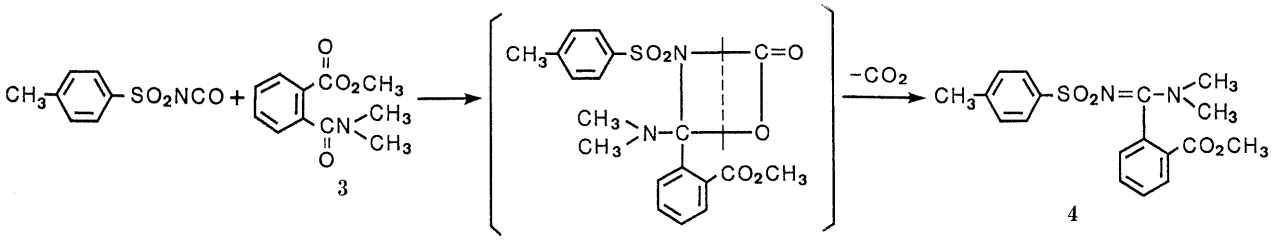


Chart 2

A new class of sulfonamide, N^2-(4-methylphenylsulfonyl)-N^1-methyl-N^1-phenylethoxalamidine (**2a**), was synthesized by reaction of **1a** with 1.5 eq of *p*-toluenesulfonyl isocyanate (TSI) in dry toluene under reflux for 25 h in 80% yield. The structure **2a** was confirmed by elemental analysis, infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectral data.

Taking into consideration this reaction, the relative reactivity of TSI was examined. Similar reaction of **1f** and **1g** with TSI also afforded **2i** and **2j** in 49% and 22% yields, respectively. Compound **2i** was formed only in dry xylene under reflux for 20 h. No side reaction, however, was observed. These low yields suggested that the electron-rich and less crowded carbonyl group of **1** would be favorable for the reaction with ASI. Reaction of **1** with ASI yielded the products **2** as summarized in Tables III and IV.

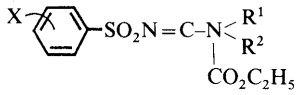
In the IR spectra the adduct **2** showed C=O (1740 cm^{-1}) and C=N (1550 cm^{-1}) absorption bands, but the C=O (1650 cm^{-1}) band which corresponded to the amide group of **1** had disappeared. The mechanism of the formation of **2** may involve addition of ASI to the amide carbonyl group

Table II. Spectral Data for *N*,*N*-Disubstituted Ethyl Oxamates (**1a—g**)

	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (–N–C(=O)–C(=O)–O–)	^{1}H-NMR ($CDCl_3$) δ (ppm)
1a[a]		
1b	1662, 1740	1.07 (3H, t, J=7 Hz), 3.33 (3H, s), 4.07 (2H, q, J=7 Hz), 7.07—7.73 (4H, m)
1c[b]		
1d[a]		
1e	1665, 1740	0.95 (3H, t, J=7 Hz), 2.33 (3H, s), 3.27 (3H, s), 3.97 (2H, q, J=7 Hz)
1f	1670, 1740	1.03 (3H, t, J=7 Hz), 3.40 (3H, s), 4.03 (2H, q, J=7 Hz), 7.17—7.80 (2H, m), 8.43—8.67 (2H, m)
1g	1670, 1740	1.03 (3H, t, J=7 Hz), 4.07 (2H, q, J=7 Hz), 7.17—7.67 (10H, m)

a, *b*) See footnotes to Table I.

Table III. N^2-Arylsulfonyl-N^1,N^1-disubstituted Ethoxalamidines (**2a—j**)



	R^1	R^2	X	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	Phenyl	Methyl	4-Methyl	139—142	81	$C_{18}H_{20}N_2O_4S$	59.98 (60.11)	5.59 5.61	7.77 7.72)
2b	Phenyl	Methyl	H	125—126	71	$C_{17}H_{18}N_2O_4S$	58.94 (58.81)	5.24 5.21	8.09 8.10)
2c	Phenyl	Methyl	4-Chloro	130—131	85	$C_{17}H_{17}ClN_2O_4S$	53.61 (53.51)	4.50 4.45	7.36 7.27)
2d	Phenyl	Methyl	2-Chloro	Oil	66	$C_{17}H_{17}ClN_2O_4S$	53.61 (53.39)	4.50 4.56	7.36 7.15)
2e	4-Chlorophenyl	Methyl	4-Methyl	134—135	80	$C_{18}H_{19}ClN_2O_4S$	54.75 (54.55)	4.85 4.84	7.09 7.05)
2f	2-Chlorophenyl	Methyl	4-Methyl	137—138	69	$C_{18}H_{19}ClN_2O_4S$	54.75 (54.63)	4.85 4.85	7.09 7.15)
2g	4-Methoxyphenyl	Methyl	4-Methyl	151—152	63	$C_{19}H_{22}N_2O_5S$	58.45 (58.22)	5.68 5.66	7.17 7.15)
2h	2-Methylphenyl	Methyl	4-Methyl	141—143	80	$C_{19}H_{22}N_2O_4S$	60.94 (60.90)	5.92 5.93	7.48 7.44)
2i	3-Pyridyl	Methyl	4-Methyl	Amorphous	49	$C_{17}H_{19}N_3O_4S$	56.50 (56.24)	5.30 5.26	11.63 11.67)
2j	Phenyl	Phenyl	4-Methyl	Amorphous	22	$C_{23}H_{22}N_2O_4S$	65.38 (65.25)	5.25 5.30	6.63 6.57)

Table IV. Spectral Data for N^2-Arylsulfonyl-N^1,N^1-disubstituted Ethoxalamidines (**2a—j**)

	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (–N(–)–C(=O)–C(=O)–O–)	^{1}H-NMR ($CDCl_3$) δ (ppm)
2a	1550, 1745	1.00 (3H, t, J=7 Hz), 2.43 (3H, s), 3.38 (3H, s), 4.07 (2H, q, J=7 Hz), 7.03—8.12 (7H, m)
2b	1550, 1745	0.97 (3H, t, J=7 Hz), 3.33 (3H, s), 4.00 (2H, q, J=7 Hz), 6.97—8.13 (10H, m)
2c	1550, 1745	0.97 (3H, t, J=7 Hz), 3.37 (3H, s), 4.05 (2H, q, J=7 Hz), 7.02—8.08 (9H, m)
2d	1550, 1745	1.02 (3H, t, J=7 Hz), 3.45 (3H, s), 4.07 (2H, q, J=7 Hz), 7.13—8.30 (9H, m)
2e	1555, 1745	1.08 (3H, t, J=7 Hz), 2.45 (3H, s), 3.38 (3H, s), 4.13 (2H, q, J=7 Hz), 7.13—8.13 (8H, m)
2f	1550, 1740	1.00 (3H, t, J=7 Hz), 2.43 (3H, s), 3.32 (3H, s), 4.03 (2H, q, J=7 Hz), 7.17—8.07 (8H, m)
2g	1555, 1740	1.05 (3H, t, J=7 Hz), 2.45 (3H, s), 3.37 (3H, s), 3.83 (3H, s), 4.05 (2H, q, J=7 Hz), 6.83—8.13 (8H, m)
2h	1550, 1740	0.95 (3H, t, J=7 Hz), 2.23 (3H, s), 2.42 (3H, s), 3.27 (3H, s), 3.98 (2H, q, J=7 Hz), 6.93—8.00 (8H, m)
2i	1555, 1745	1.05 (3H, t, J=7 Hz), 2.43 (3H, s), 3.40 (3H, s), 4.11 (2H, q, J=7 Hz), 7.13—8.10 (6H, m), 8.50—8.80 (2H, m)
2j	1550, 1745	1.07 (3H, t, J=7 Hz), 2.40 (3H, s), 4.12 (2H, q, J=7 Hz), 6.94—7.88 (14H, m)

of **1** to form an unstable four-membered ring adduct, from which carbon dioxide is expelled as indicated in Chart 1.

The main point of interest was the highly selective cycloaddition reaction of ASI with two different carbonyl groups of **1**. The verification of this selective reaction was conducted by using the model compound **3**, having two reactive functional groups, *i.e.*, ester ($COOCH_3$) and amide ($CON(CH_3)_2$) groups. The amide carbonyl group in **3** readily underwent a [2+2] cycloaddition reaction with TSI. The obtained adduct **4** showed the expected spectral data. In the IR spectra the C=O band (1650 cm^{-1}) of **3** had disappeared, while the C=N (1550 cm^{-1}) of **4** had appeared. Therefore, TSI showed selective addition to the amide carbonyl group (Chart 2).

The significance of the novel cycloaddition reaction lies in the reactivity of the two different carbonyl groups with the sulfonyl isocyanates. Accordingly, our reaction can be used to prepare new N^2-arylsulfonyl-N^1,N^1-disubstituted ethoxalamidines in good yields.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were taken on a JEOL JNM-PMX60 NMR spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard, and the chemical shifts are given in δ values.

General Procedure for Preparation of Ethyl *N*,*N*-Disubstituted Oxamates (1a—g) Ethyl oxalyl chloride (2.3 g, 16.8 mmol) was added to a solution of an *N*,*N*-disubstituted amine (14.0 mmol) and triethylamine (1.7 g, 16.8 mmol) in CH_2Cl_2 (15 ml). The resulting solution was stirred at room temperature for 30 min.

After filtration, the filtrate 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 CH_2Cl_2 and $CH_3CO_2C_2H_5$ (9 : 1).

Reaction of ASI with *N*,*N*-Disubstituted Oxamates 1. **2a—h,j**: In the general procedure, a mixture of ethyl *N*,*N*-disubstituted oxamate (2.4 mmol) and ASI (3.6 mmol) in toluene (5 ml) was refluxed for 25 h. The mixture was poured into water (50 ml), extracted with CH_2Cl_2 and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography with CH_2Cl_2–hexane–$CH_3CO_2C_2H_5$ (3 : 2 : 1).

2. **2i**: A mixture of ethyl *N*-methyl-*N*-pyridyl oxamate (4.8 mmol) and TSI (5.8 mmol) in xylene (10 ml) was refluxed for 20 h. The isolation procedure was as described above.

Reaction of TSI with Methyl 2-(Dimethylcarbamoyl)benzoate A mixture of methyl 2-(dimethylcarbamoyl)benzoate **3** (2.4 mmol) and TSI (2.4 mmol) in toluene (7 ml) was refluxed for 25 h. After removal of the solvent, the residue was purified by silica gel chromatography with CH_2Cl_2 and CH_3OH (20 : 1). Recrystallization from CH_2Cl_2 and hexane gave **4** in 44% yield, mp 134—135 °C. IR ($CHCl_3$): 1555 (>C=N–), 1735 (>C=O). ^{1}H-NMR ($CDCl_3$): 2.40 (3H, s), 2.75 (3H, s), 3.32 (3H, s), 6.95—8.17 (8H, m). *Anal.* Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 60.02; H, 5.61; N, 7.73.

Registry Nos. **1a**, 1457-86-9; **1c**, 69087-20-3; **1d**, 16077-05-7.

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

References

1) Part I: T. Iwakawa, H. Tamura, T. Sato and Y. Hayase, *Chem. Pharm. Bull.*, **36**, 4755 (1988).
2) C. King, *J. Org. Chem.*, **25**, 352 (1960); G. Kresze and R. Albrecht, *Angew. Chem.*, **74**, 781 (1962); R. Albrecht, G. Kresze and B. Mlakar, *Chem. Ber.*, **97**, 483 (1964); H. Ulrich, B. Tucker and A. A. R. Sayigh, *Angew. Chem., Int. Ed. Engl.*, **7**, 291 (1968); E. Schaumann, E. Kausch and J. P. Imbert, *Chem. Ber.*, **111**, 1475 (1978); D. Ndhar and A. Kbag, *Indian J. Chem.*, **22B**, 627 (1983); M. Baillarge and F. L. Goffic, *Synth. Commun.*, **17**, 1603 (1987); K. R. Rao, Y. V. D. Nageswar, T. N. Srinivasan and P. B. Sattur, *ibid.*, **18**, 877 (1988).