A NEW SYNTHESIS OF 5,6-DIHYDRO-4H-1,3,4-THIADIAZINE 1,1-DIOXIDES FROM METHYL STYRYLSULFONYLACETATE

Masahiko Takahashi* and Ichiro Yamashita
Department of Industrial Chemistry, Faculty of Engineering,
Ibaraki University, Hitachi, Ibaraki 316, Japan

Abstract————Treatment of methyl styrylsulfonylacetate with arenediazonium chlorides gave methyl styrylsulfonylglyoxylate arenehydrazones, which were cyclized on treatment with bases to 4-aryl-5-phenyl-5,6-dihydro-1,3,4-thiadiazine 1,1-dioxides, a hitherto unknown class of heterocycles.

In the previous papers we have shown that β-keto, β-cyano, and β-ethoxycarbonyl-β-sulfonylenamines are good building blocks for 5-sulfonylpyrimidines,[1] 4-sulfonylpyrazoles,[2] and 4-sulfonylisoxazoles. As an extension of this work we took an interest in the related enamine, β-vinylsulfonyl-β-methoxycarbonylenamine (3). Although divinylsulfones are reported to cyclize on treatment with amines to 2,3,5,6-tetrahydro-1,4-thiazine 1,1-dioxides,[3] functionalized vinylsulfonylenamine such as 3 seems to give relatively undeveloped heterocycles, 2,3-dihydro-1,4-thiazine 1,1-dioxides (4)[4] on substitution of the dimethylamino group by amines followed by intramolecular Michael type addition. As (Z)-styrylsulfonylacetic acid (1) has become readily available recently from phenylacetylene and thioglycolic acid,[5] we have tried to prepare 4 from 1. The acid (1) was methylated in a usual manner to give methyl ester (2) in 52% yield. The ester (2) was converted on treatment with N,N-dimethylformamide dimethylacetal in refluxing methanol to vinylsulfonylenamine (3) in 77% yield. In the preliminary experiment this enamine (3) reacted with acetamidine similarly to the previously reported sulfonylenamines[1] to yield 5-styrylsulfonylpyrimidinone (5). However, all attempts to substitute the dimethylamino group of 3 by primary amines followed by cyclization to 4 were unsuccesful.

Next, we intended to prepare the aza analogue of 4, 5,6-dihydro-1,3,4-thiadiazine 1,1-dioxide (8) from 2. Since 5,6-dihydro-1,2,4-thiadiazine 1,1-dioxides (6) have been obtained from styrylsulfonyl chloride and amidines (R=H, X=alkyl or aryl),[6] or N-styrylsulfonyl-S-

methylisothioureas (R=alkyl, X=SMe),[7] hydrazones (7) are expected to give 8 in a similar fashion. Treatment of a solution of 2 in pyridine with arenediazonium chlorides in a usual manner gave methyl styrylsulfonylglyoxylate arylhydrazones (7a-h) in 32-84% yields (Tables 1 and 2). Cyclization of 7a and c-f was achieved in 38-77% yields by refluxing a mixture of 7 and triethylamine in methanol for 3-11 h. Hydrazone (7b) could be cyclized to 8b when 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) was used as a base, while the products from 7g and h were difficult to purify. The structures of the products were unambigously revealed by the ^{1}H-nmr spectra; 8a exhibited a doublet at δ 3.74 and a triplet at δ 5.97 ppm ascribable to the protons at the C-6 and C-5 positions, respectively, and other products (8b, c, e, and f) also showed the same A_2X patterns (J_{AX}=5 Hz). On the other hand, the ring protons of 8d in the nmr spectrum were observed in an ABX pattern similar to those of 6[6,7] probably due to inhibition of ring inversion by the bulky o-chlorophenyl substituent. In spite of the well-known chemistry of 1,3,4-thiadiazines[8] no attention has been paid to their 1,1-dioxides.[9] To our knowledge no preparative methods of the 1,1-dioxides have been reported yet and our results reported here appear to be the first example of 1,3,4-thiadiazine 1,1-dioxides.

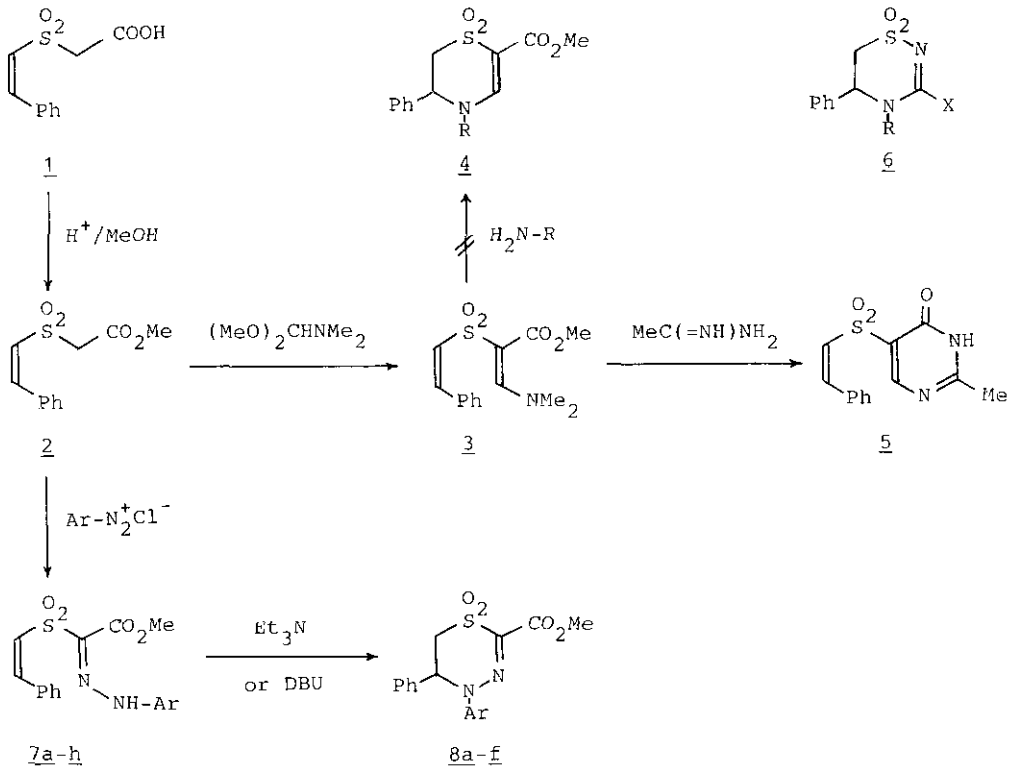

Table 1. Physical and analytical data of compounds 7 and 8

Compounds	Ar	Yield %	mp/°C (Solvent)	Molecular Formula (mw)	Found % (Calcd %) C	H	N
7a	C_6H_5	84	117-119 (MeOH)	$C_{17}H_{16}N_2O_4S$ (344.48)	59.31 (59.29	4.82 4.68	8.13 8.13)
7b	4-MeC_6H_4	44	125-127 (MeOH)	$C_{18}H_{18}N_2O_4S$ (358.41)	60.48 (60.32	5.01 5.06	7.77 7.82)
7c	4-ClC_6H_4	61	128-130 (MeOH)	$C_{17}H_{15}N_2O_4ClS$ (378.83)	53.80 (53.90	7.30 7.39	4.09 3.99)
7d	2-ClC_6H_4	79	135-137 (MeOH)	$C_{17}H_{15}N_2O_4ClS$ (378.83)	53.84 (53.90	3.95 3.99	7.22 7.39)
7e	3,4-$Cl_2C_6H_3$	47	140-142 (MeOH)	$C_{17}H_{14}N_2O_4Cl_2S$ (413.27)	49.58 (49.41	3.47 3.41	6.62 6.78)
7f	4-BrC_6H_4	42	141-142 (MeOH)	$C_{17}H_{15}N_2O_4BrS$ (423.28)	48.20 (48.24	3.84 3.57	6.48 6.62)
7g	4-$NO_2C_6H_4$	57	154-156 (MeOH)	$C_{17}H_{15}N_3O_6S$ (389.38)	52.22 (52.44	4.18 3.88	10.76 10.79)
7h	4-$MeOC_6H_4$	32	128-130 (MeOH)	$C_{18}H_{18}N_2O_5S$ (374.41)	57.49 (57.74	4.88 4.84	7.37 7.48)
8a	C_6H_5	77	196-198 (MeOH)	$C_{17}H_{16}N_2O_4S$ (344.38)	59.29 (59.29	4.86 4.68	8.13 8.13)
8b	4-MeC_6H_4	38	158-160 (MeOH)	$C_{18}H_{18}N_2O_4S$ (358.41)	60.30 (60.32	5.07 5.06	7.64 7.82)
8c	4-ClC_6H_4	46	185-187 (MeOH)	$C_{17}H_{15}N_2O_4ClS$ (378.83)	53.90 (53.90	4.28 3.99	7.32 7.39)
8d	2-ClC_6H_4	38	178-180 (MeOH)	$C_{17}H_{15}N_2O_4ClS$ (378.83)	53.90 (53.90	4.02 3.99	7.17 7.39)
8e	3,4-$Cl_2C_6H_3$	39	197-199 (MeOH)	$C_{17}H_{14}N_2O_4Cl_2S$ (413.27)	49.48 (49.41	3.46 3.41	6.63 6.78)
8f	4-BrC_6H_4	70	210-212 ($MeOH-CHCl_3$)	$C_{17}H_{15}N_2O_4BrS$ (423.28)	47.98 (48.24	3.79 3.57	6.55 6.62)

Table 2. Spectral data of compounds 7 and 8

Com-pounds	Ms m/z (M^+)	Ir KBr, cm^{-1}			^1H-Nmr δ, ppm (solvent)
7a	344	3170	1680	1600	3.87 (s, 3 H), 6.80 (d, J=12 Hz, 1 H), 7.14-7.75
		1525	1460	1315	(m, 11 H), 12.27 (br s, 1 H) (acetone-d_6)
7b	358	3160	1680	1595	2.10 (s, 3 H), 3.60 (s, 3 H), 6.32 (d, J=12 Hz, 1 H),
		1520	1440	1315	6.75-7.42 (m, 10 H), 12.18 (br s, 1 H) ($CDCl_3$)
7c	378	3250	1700	1600	3.60 (s, 3 H), 6.31 (d, J=12 Hz, 1 H), 6.78-7.40 (m,
		1490	1290	1220	10 H), 12.10 (br s, 1 H) ($CDCl_3$)
7d	378	3170	1690	1535	3.88 (s, 3 H), 6.57 (d, J=12 Hz, 1 H), 7.03-7.74 (m,
		1330	1240	1155	10 H), 12.74 (br s, 1 H) ($CDCl_3$)
7e	412	3250	1705	1600	3.62 (s, 3 H), 6.30 (d, J=12 Hz, 1 H), 6.78-7.38 (m,
		1570	1510	1480	9 H), 12.04 (br s, 1 H) ($CDCl_3$)
7f	422	3230	1675	1520	3.59 (s, 3 H), 6.31 (d, J=12 Hz, 1 H), 6.75-7.38 (m,
		1490	1440	1330	10 H), 12.08 (br s, 1 H) ($CDCl_3$)
7g	389	3250	1715	1595	3.64 (s, 3 H), 6.58 (d, J=12 Hz, 1 H), 7.02-7.35 (m,
		1535	1500	1335	6 H), 7.39 (d, J=9 Hz, 2 H), 8.02 (d, J=9 Hz, 2 H),
					11.95 (br s, 1 H) (DMSO-d_6)
7h	374	3160	1680	1600	3.79 (s, 3 H), 3.84 (s, 3 H), 6.57 (d, J=12 Hz, 1 H),
		1530	1435	1400	6.78-7.66 (m, 10 H), 12.54 (br s, 1 H) ($CDCl_3$)
8a	344	1695	1530	1490	3.74 (d, J=5 Hz, 2 H), 3.89 (s, 3 H), 5.97 (t, J=5
		1450	1435	1310	Hz, 1 H), 7.07-7.41 (m, 9 H) ($CDCl_3$)
8b	358	1690	1495	1430	2.25 (s, 3 H), 3.72 (d, J=5 Hz, 2 H), 3.88 (s, 3 H),
		1310	1250	1220	5.92 (t, J=5 Hz, 1 H), 7.05-7.33 (m, 9 H) ($CDCl_3$)
8c	378	1725	1525	1490	3.72 (d, J=5 Hz, 2 H), 3.87 (s, 3 H), 5.90 (t, J=5
		1450	1435	1320	Hz, 1 H), 7.02-7.35 (m, 9 H) ($CDCl_3$)
8d	378	1710	1525	1480	3.52 (dd, J=3 and 14 Hz, 1 H), 3.88 (s, 3 H), 4.00
		1440	1335	1305	(dd, J=12 and 14 Hz, 1 H), 5.80 (dd, J=3 and 12 Hz,
					1 H), 7.02-7.20 (m, 9 H) ($CDCl_3$)
8e	412	1735	1540	1475	3.75 (d, J=5 Hz, 2 H), 3.90 (s, 3 H), 5.89 (t, J=5
		1435	1320	1270	Hz, 1 H), 7.03-7.38 (m, 8 H) ($CDCl_3$)
8f	422	1720	1530	1490	3.75 (d, J=5 Hz, 2 H), 3.91 (s, 3 H), 5.90 (t, J=5
		1435	1320	1260	Hz, 1 H), 7.00-7.22 (m, 9 H) ($CDCl_3$)

EXPERIMENTAL

Melting points were determined by using a Yanaco micromelting point apparatus. Ir spectra were obtained on a *JASCO A-102 spectrophotometer*. Mass and ^{1}H-nmr spectra were determined on a JEOL JMS-DX 300 spectrometer and JEOL JMN-PMX 60 spectrometer, respectively. Microanalyses were carried out with a Yanaco CHN CODER MT-5.

Methyl (Z)-styrylsulfonylacetate (2) A mixture of 1[5] (158 mg, 0.70 mmol) and one drop of concentrated sulfuric acid in MeOH (15 ml) was refluxed for 15 h. After removal of the solvent the residue was recrystallized from MeOH to give 2 (88 mg, 52%), mp 79-81°C. Ir (KBr): 1740, 1610, 1440, 1300, 1280, 1160 cm^{-1}. ^{1}H-Nmr (acetone-d_6): δ 3.68 (s, 3 H), 4.19 (s, 2 H), 6.73 (d, J=12 Hz, 1 H), 7.18-7.74 (m, 6 H). Ms: m/z 240 (M$^+$). Anal. Calcd for $C_{11}H_{12}O_4S$: C 55.00; H, 5.04. Found: C, 54.72; H, 5.01.

Methyl 3-dimethylamino-2-[(Z)-styrylsulfonyl]propenoate (3) A mixture of 2 (2.4 g, 10 mmol) and N,N-dimethylformamide dimethylacetal (4.8 g, 40 mmol) in MeOH (5 ml) was refluxed for 7 h. After evaporation of the solvent the residue was column chromatographed on silica gel using $CHCl_3$ as an eluent to remove excess dimethylacetal. The product obtained from the main elution band was recrystallized from ethyl acetate to give 3 (2.3 g, 77%), mp 109-112°C. Ir (KBr): 1690, 1615, 1435, 1410, 1375, 1290 cm^{-1}. ^{1}H-Nmr (acetone-d_6): δ 2.95 (br s, 6 H), 3.59 (s, 3 H), 6.60 (d, J=12 Hz, 1 H), 6.96 (d, J=12 Hz, 1 H), 7.22-7.63 (m, 6H). Ms: m/z 295 (M$^+$). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.68; H, 5.74; N, 4.57.

2-Methyl-5-[(Z)-styrylsulfonyl]pyrimidin-4-one (5) A mixture of 3 (200 mg, 0.68 mmol), acetamidine hydrochloride (83 mg, 0.88 mmol), and sodium carbonate (47 mg, 0.44 mmol) in a mixed solvent (MeOH 8 ml and water 3 ml) was refluxed for 8 h. After evaporation of the solvent the residue was neutralized with aq. acetic acid, and the precipitates formed were collected and recrystallized from MeOH to give 5 (38 mg, 20%), mp 250-252°C. Ir (KBr): 3050-2630, 1620, 1550, 1480, 1445 cm^{-1}. ^{1}H-Nmr (DMSO-d_6): δ 2.37 (s, 3 H), 7.17-7.76 (m, 7 H), 8.39 (s, 1 H). Ms: m/z 276 (M$^+$). Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.36; H, 4.32; N, 10.07.

Methyl (Z)-styrylsulfonylglyoxylate arylhydrazones (7a-h)

A general procedure. To a solution of 2 (1.5 mmol) in pyridine (5 ml) which was stirred and cooled below 5°C, aq. arenediazonium chloride (2.5 mmol) prepared in a usual manner was added dropwise. After additional stirring for 1 h the precipitates formed were collected and recrystallized to give 7.

Methyl 4-aryl-5-phenyl-5,6-dihydro-1,3,4-thiadiazine 1,1-dioxide-2-carboxylates (8a-f)

A general procedure for 8a and c-f. A mixture of 7 (0.40 mmol) and excess triethylamine

(4.0 mmol) in MeOH (8 ml) was refluxed for 3-11 h. After evaporation of the solvent the residue was recrystallized to give 8.

A procedure for 8b. A mixture of 7b (200 mg, 0.54 mmol) and DBU (60 mg, 0.39 mmol) in MeOH (8 ml) was refluxed for 5 h. After evaporation of the solvent the residue was recrystallized to give 8b.

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