A New Cyclisation Involving a Methanesulfinyl Leaving Group Yielding 6-Sulfenylated 2-Amino-4*H*-5,6-dihydro-1,3,4-thiadiazines

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Nucleophilic addition of sulfenylated dimethyl sulfoxide derivatives to thiosemicarbazones **3** followed by a new intramolecular cyclisation involving an acid labile methanesulfinyl leaving group yields 6-sulfenylated 2-amino-5-aryl-4*H*,5,6-dihydro-1,3,4-thiadiazines **6**.

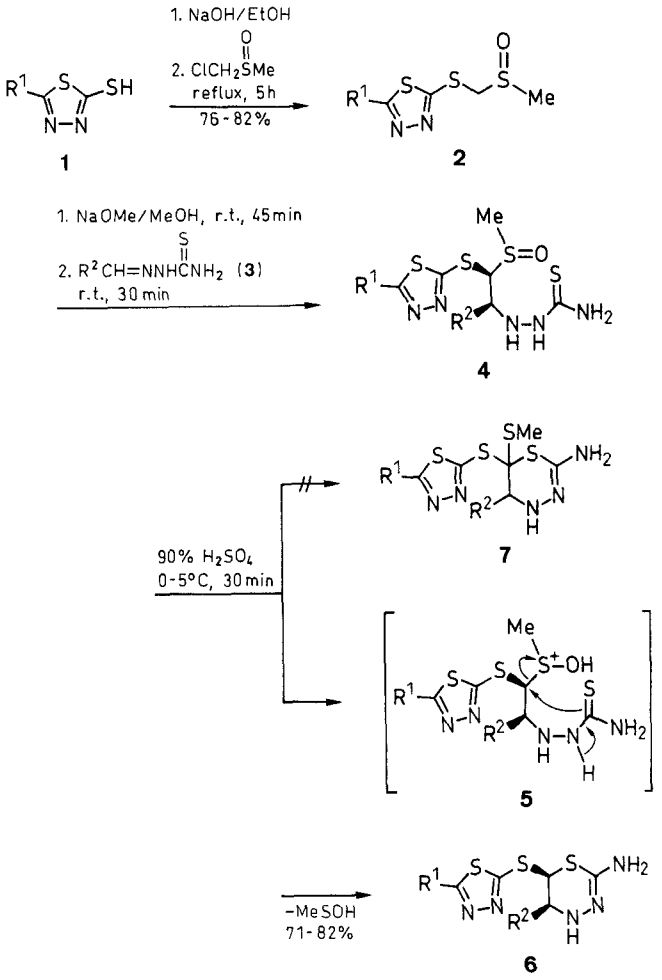
In view of the biological potential of 1,3,4-thiadiazine derivatives as cardiac tonics and antihypertensives,[1,2] muscle relaxants,[3,4] herbicides,[5,6] fungicides[7,8] and insecticides,[9] and the unexplored chemistry and bioactivity of 6-sulfenylated as well as partially hydrogenated 2-amino-4*H*-5,6-dihydro-1,3,4-thiadiazines **6**, we have devised their direct synthesis. It is noteworthy that 1,3,4-thiadiazines of the type **6** are hitherto unreported and are not accessible through any one of the known synthetic routes for 1,3,4-thiadiazines.[1-9]

After some preliminary experimentation, it was found that the envisaged synthesis was successful with adducts **4**, where methanesulfinyl group functions as an efficient acid labile leaving group (Scheme). The formation of adducts **4** and their cyclisation to **6** were highly diastereoselective. Crude products were checked by ^{1}H NMR to avoid false conclusions through modification of diastereoisomer ratios during isolation and purification (see experimental details).

The reaction of chloromethyl methyl sulfoxide and the sodium salt of 5-aryl-2-mercapto-1,3,4-thiadiazoles **1** in refluxing ethanol for 5 hours furnished **2**. Nucleophilic addition of sulfur-stabilised carbanions, generated by the action of sodium methoxide on **2** in methanol at room temperature, to C=N of thiosemicarbazones **3** followed by quenching with dilute hydrochloric acid afforded **4** in 71–82% yield with high diastereoselectivity (92–96%). Adducts **4** underwent a new intramolecular cyclisation, involving the acid labile methanesulfinyl leaving group, on treatment with 90% sulfuric acid at 0–5°C to furnish **6** in high yields (71–82%) with 94–97% diastereoselectivity (Table). It is interesting to note that the Pummerer rearrangement products **7** were not obtained at all during the present synthesis.

The easy and wide availability of the requisite substrates, and simple operations under mild conditions make the present cyclisation a general synthetic method for a variety of cyclic systems. Various syntheses employing the acid labile methanesulfinyl leaving group are now in progress.

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer in DMSO-d_6 using TMS as an internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer.



1,2	R^1	3	R^2
a	Ph	a	Ph
b	2-ClC$_6$H$_4$	b	4-ClC$_6$H$_4$
c	4-ClC$_6$H$_4$	c	3-NO$_2$C$_6$H$_4$

4,6	R^1	R^2	4,6	R^1	R^2
a	Ph	Ph	f	2-ClC$_6$H$_4$	3-NO$_2$C$_6$H$_4$
b	Ph	4-ClC$_6$H$_4$	g	4-ClC$_6$H$_4$	Ph
c	Ph	3-ClC$_6$H$_4$	h	4-ClC$_6$H$_4$	4-ClC$_6$H$_4$
d	2-ClC$_6$H$_4$	2-ClC$_6$H$_4$	i	4-ClC$_6$H$_4$	3-NO$_2$C$_6$H$_4$
e	2-ClC$_6$H$_4$	2-ClC$_6$H$_4$			

Scheme

5-Aryl-2-methylsulfinylmethylthio-1,3,4-thiadiazoles 2; General Procedure:

To a solution of 2-mercapto-1,3,4-thiadiazole[10] **1** (20 mmol) and NaOH (0.80 g, 20 mmol) in EtOH (50 mL) was added chloromethyl

Table. Compounds **2,4** and **6** Prepared

Product[a]	Yield[b] (%)	mp (°C)	IR (KBr)[c] ν (cm^{-1})	^1H NMR (DMSO-d_6/TMS) δ, J (Hz)	MS m/z (M^+)
2a	82	161–162	1030	2.61 (s, 3H), 4.25 (s, 2H), 7.33–7.78 (m, 5H)	270
2b	80	131	1040	2.62 (s, 3H), 4.28 (s, 2H), 7.38–8.01 (m, 4H)	304
2c	78	171–172	1035	2.62 (s, 3H), 4.27 (s, 2H), 7.36–8.00 (m, 4H)	304
4a	78	160–162	1030	2.59 (s, 3H), 3.73 (d, 1H, J = 4), 4.94 (d, 1H, J = 4), 7.34–7.79 (m, 10H), 8.40–9.15 (br, 4H)	449
4b	75	164–165	1030	2.58 (s, 3H), 3.75 (d, 1H, J = 4), 4.98 (d, 1H, J = 4), 7.30–8.04 (m, 9H), 8.44–9.18 (br, 4H)	483
4c	73	177	1030	2.56 (s, 3H), 3.73 (d, 1H, J = 4), 5.02 (d, 1H, J = 4), 7.32–8.12 (m, 9H), 8.48–9.22 (br, 4H)	494
4d	72	103	1035	2.58 (s, 3H), 3.72 (d, 1H, J = 4), 4.93 (d, 1H, J = 4), 7.30–8.06 (m, 9H), 8.42–9.16 (br, 4H)	483
4e	75	200–203	1035	2.59 (s, 3H), 3.76 (d, 1H, J = 4), 5.00 (d, 1H, J = 4), 7.36–8.06 (m, 8H), 8.45–9.19 (br, 4H)	517
4f	71	146–148	1035	2.58 (s, 3H), 3.75 (d, 1H, J = 4), 5.04 (d, 1H, J = 4), 7.34–8.16 (m, 8H), 8.51–9.24 (br, 4H)	528
4g	80	127–128	1035	2.58 (s, 3H), 3.73 (d, 1H, J = 4), 4.94 (d, 1H, J = 4), 7.31–8.08 (m, 9H), 8.42–9.18 (br, 4H)	483
4h	82	159–160	1035	2.60 (s, 3H), 3.76 (d, 1H, J = 4), 5.01 (d, 1H, J = 4), 7.35–8.08 (m, 8H), 8.46–9.21 (br, 4H)	517
4i	76	183–185	1035	2.59 (s, 3H), 3.77 (d, 1H, J = 4), 5.05 (d, 1H, J = 4), 7.36–8.18 (m, 8H), 8.53–9.23 (br, 4H)	528
6a	82	103	3320, 3375	4.13 (d, 1H, J = 4), 5.20 (d, 1H, J = 4), 7.33–7.76 (m, 10H), 4.54–4.71 (br, 3H)	305
6b	80	165–166	3315, 3365	4.15 (d, 1H, J = 4), 5.18 (d, 1H, J = 4), 7.30–8.09 (m, 9H), 4.59–4.78 (br, 3H)	419
6c	77	160–161	3310, 3360	4.14 (d, 1H), 5.29 (d, 1H, J = 4), 7.33–8.15 (m, 9H), 4.61–4.81 (br, 3H)	430
6d	78	78	3315, 3375	4.20 (d, 1H, J = 4), 5.31 (d, 1H, J = 4), 7.32–8.12 (m, 9H), 4.57–4.74 (br, 3H)	419
6e	76	139	3310, 3365	4.24 (d, 1H, J = 4), 5.26 (d, 1H, J = 4), 7.33–8.01 (m, 8H), 4.61–4.81 (br, 3H)	453
6f	73	196	3310, 3355	4.14 (d, 1H, J = 4), 5.24 (d, 1H, J = 4), 7.36–8.14 (m, 8H), 4.64–4.83 (br, 3H)	500
6g	76	85–86	3320, 3370	3.12 (d, 1H, J = 4), 5.12 (d, 1H, J = 4), 7.32–8.10 (m, 9H), 4.59–4.75 (br, 3H)	419
6h	74	184	3315, 3365	4.15 (d, 1H, J = 4), 5.28 (d, 1H, J = 4), 7.38–8.10 (m, 8H), 4.62–4.84 (br, 3H)	453
6i	71	120–121	3315, 3355	4.16 (d, 1H, J = 4), 5.31 (d, 1H, J = 4), 7.30–8.12 (m, 9H), 4.66–4.84 (br, 3H)	500

[a] All compounds are new and gave satisfactory microanalyses: C ± 0.30, H ± 0.18, N ± 0.22.
[b] Yield of isolated and purified product.
[c] ν-Values refer to S = O group in the cases of **2a–c, 4a–i** and $NHNH_2$ in the cases of **6a–i**.

methyl sulfoxide[11] (2.25 g, 20 mmol) and the mixture was refluxed for 5 h. The solvent was evaporated, the residue thus obtained was washed with H_2O and recrystallised from EtOH to afford pure **2** (Table).

1-[(1-Aryl)-2-(5-aryl-1,3,4-thiadiazol-2-ylthio)-2-methylsulfinyl)ethyl]-thiosemicarbazides 4; General Procedure:
To a solution of NaOMe (1.08 g, 20 mmol) in MeOH (50 mL) was added **2** (10 mmol), and after stirring the reaction mixture at r.t. for 45 min, semicarbazone **3** (10 mmol) was added. The mixture was further stirred at r.t. for 1 h followed by stirring at 50–60 °C for 30 min, then it was quenched with H_2O (50 mL) and acidified with 5 M HCl (4.4 mL) just to neutrality. The product thus precipitated was recrystallised from EtOH to give a diastereoisomeric mixture (> 97: < 3; in the crude products the ratio was 92–96:8-4, determined by ^1H NMR spectroscopy) which was again recrystallised from EtOH to obtain an analytical sample of a single diastereoisomer **4**. On the basis of ^1H NMR and the general literature precedent,[12–14] compounds **4** were assigned the erythro (syn) stereochemistry, as their ^1H NMR spectra exhibited a lower value of coupling constant, $J_{SCH,NCH}$ = 4 Hz, than that for the very minor (< 3 %) diastereoisomer (*threo* or *anti*), $J_{SCH,NCH}$ = 10 Hz (Table).

2-Amino-5-aryl-6-(5-aryl-1,3,4-thiadiazol-2-ylthio)-4*H*-5,6-dihydro-1,3,4-thiadiazines 6; General Procedure:
Appropriate compound **4** (5 mmol) was dissolved in 90 % H_2SO_4 (10 mL) under ice-cooling (maintaining the temperature of the reaction mixture at < 5 °C) and allowed to stand in an ice-bath for 30 min. The product was isolated by pouring the mixture into H_2O (50 mL) followed by basification with conc. NH_4OH (7.0 mL). It was recrystallised from EtOH to give a mixture of diastereoisomers (> 98: < 2; in the crude products the ratio was 94–97:6-3, determined by ^1H NMR spectroscopy) which on second recrystallisation from EtOH furnished an analytical sample of a single diastereoisomer **6**. Compounds **6** were assigned cis stereochemistry, as the coupling constant, $J_{5,6}$ = 4 Hz, for **6** was lower than that for the very minor (< 2 %) diastereoisomer (*trans*), $J_{5,6}$ = 10 Hz[12,15,16] (Table).

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