1-(Arylthio)methanesulfonamides

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The synthesis of 1-(arylthio)methanesulfonamides by the reaction of sodium arylthiolates with 1-bromomethanesulfonamides is described. The sulfide linkage of the 1-(arylthio)methanesulfonamides is readily oxidized: two equivalents of 30% hydrogen peroxide in refluxing glacial acetic acid affording 1-(arylsulfonyl)methanesulfonamides, and stepwise addition of 30% hydrogen peroxide in glacial acetic acid at 65–70° affording 1-(arylsulfinyl)methanesulfonamides. The 1-(arylthio)methanesulfonamides and 1-(arylsulfonyl)methanesulfonamides undergo halogenation of the methylene group to give the corresponding dihalo derivatives.

Although a convenient procedure exists for the synthesis of 1-(methylsulfonyl)methanesulfonamides (**1**) (*3*), other methanesulfonamides bearing a sulfur-containing substituent in the α-position have received only brief attention (*4*). In this paper, we will discuss the synthesis and chemistry of 1-(arylthio)methanesulfonamides (**5**).

$$CH_3SO_2CH_2SO_2NR^1R^2$$
1

Reaction of bromomethanesulfonyl chloride (**2**) (*5*) with two equivalents of a primary or secondary amine afforded the corresponding bromomethanesulfonamide (**3**, Table I, Equation 1). Reaction of **3**

$$\underset{\mathbf{2}}{BrCH_2SO_2Cl} + 2\,R^1R^2NH \xrightarrow{ClCH_2Cl} \underset{\mathbf{3}}{BrCH_2SO_2NR^1R^2} \quad (1)$$

with two equivalents of the sodium salt of a benzenethiol (**4**) in refluxing methanol afforded the corresponding 1-(arylthio)methanesulfonamide (**5**, Table II, Equation 2). The yields of **5** varied from 11 to 87% and appear to be somewhat dependent on the

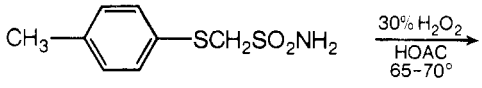
$$\underset{\mathbf{4}}{2ArS^-Na^+} + BrCH_2SO_2NR^1R^2 \xrightarrow[\text{reflux}]{CH_3OH} \underset{\mathbf{5}}{ArSCH_2SO_2NR^1R^2} \quad (2)$$

nature of the substituents on the benzenethiol and the sulfonamide substituents R^1 and R^2.

The 1-(arylthio)methanesulfonamides readily undergo oxidation of the sulfide linkage to give sulfones and sulfoxides. Thus, treatment of **5** with two equivalents of 30% hydrogen peroxide in refluxing glacial acetic acid afforded the corresponding 1-(arylsulfonyl)methanesulfonamides (**6**, Table III, Equation 3). In contrast,

$$\mathbf{5} \xrightarrow[HOAC,\,reflux]{30\%\,H_2O_2} \underset{\mathbf{6}}{ArSO_2CH_2SO_2NR^1R^2} \quad (3)$$

controlled oxidation of 1-[(4-methylphenyl)thio]methanesulfonamide (**7**) and 1-[(3,4-dichlorophenyl)thio]methanesulfonamide (**8**), with 30% hydrogen peroxide in glacial acetic acid at 65–70° afforded the corresponding sulfoxides **9** (Equation 4) and **10** (Equation 5), respectively.



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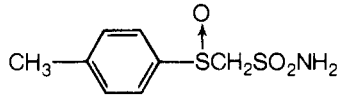

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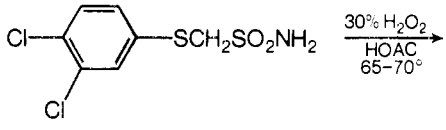

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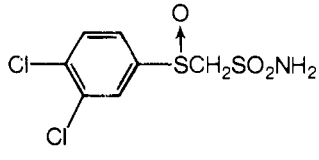

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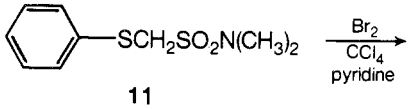
The 100 MHz proton magnetic resonance spectra of **9** and **10** (DMSO-d_6) display AB quartets for the methylene protons with chemical shifts of 4.42 δ and 4.61 δ and a geminal coupling constant of 13.5 Hz for **9** and chemical shifts of 4.58 δ and 4.83 δ and a geminal coupling constant of 13.6 Hz of **10.**

The 1-(arylthio)methanesulfonamides (**5**) and their sulfone analogs (**6**) undergo halogenation at the activated methylene group to give the corresponding dihalo derivatives. Thus, treatment of *N,N*-dimethyl-1-(phenylthio)methanesulfonamide (**11**) with bromine and pyridine in carbon tetrachloride for 19 h afforded a 48% yield of 1,1-dibromo-*N,N*-dimethyl-1-(phenylthio)methanesulfonamide (**12,** Equation 6). As would be expected, the sulfone analogs underwent



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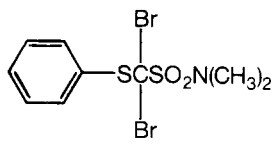

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12

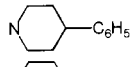
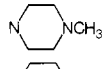
halogenation more easily and rapidly. Treatment of *N,N*-dimethyl-1-(phenylsulfonyl)methanesulfonamide (**13**) with bromine in aqueous sodium hydroxide for 30 min gave an 84% yield of 1,1-dibromo-*N,N*-dimethyl-1-(phenylsulfonyl)-methanesulfonamide (**14,** Equation 7).

Table I. 1-Bromomethanesulfonamides (3)[a]

R^1	R^2	Yield, %	Mp, °C
H	H	72	120–121.5
H	C_6H_5	53	73–75[b]
CH_3	CH_3	74	95–96
$CH_2CH_2CH_2CH_2CH_2$		71	99–100
$CH_2CH_2OCH_2CH_2$		77	132–134[c]
$CH_2CH_2NCH_2CH_2$		72	104–105
	CH_3		
$CH_2CH_2CHCH_2CH_2$		64	155–157
	C_6H_5		

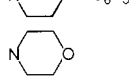
[a] Elemental analyses (for these compounds) in agreement with theoretical values were obtained and submitted for review. [b] Ref. *1*, mp 77°. [c] Ref. *6*, mp 133–135°.

Table II. 1-(Arylthio)methanesulfonamides (5)[a]

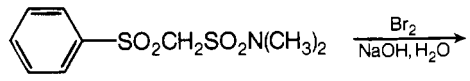
Ar	NR^1R^2	Yield, %	Mp, °C	—CH_2— chemical shift, δ[b]
4-$CH_3C_6H_4$	NH_2	75	122–124	4.394[c]
3-$CF_3C_6H_4$[d]	NH_2	11	76–77	4.571[e]
3,4-$Cl_2C_6H_3$	NH_2	63	102–104	4.548[c]
2,4,5-$Cl_3C_6H_2$	NH_2	30	159–161	4.646[c]
C_6H_5	NHC_6H_5	28	75–77	4.285
C_6H_5	$N(CH_3)_2$	87	71–72	...
4-$CH_3OC_6H_4$	$N(CH_3)_2$	55	65.5–67	4.158[e]
4-$(CH_3)_3CC_6H_4$		82	68–70	4.206[e]
C_6H_5		47	109.5–110.5	4.286[e]
C_6H_5		44	123–124	4.255[e]
C_6H_5		25	118–120	4.270[e]
4-ClC_6H_4		73	143–144.5	4.216[e]

[a] Elemental analyses (for these compounds) in agreement with theoretical values were obtained and submitted for review. [b] Values are ±0.002 δ. [c] The solvent was acetone–d_6. [d] The chemical shift of the trifluoromethyl group is 62.41 ppm relative to $CFCl_3$ at 56.4 MHz in $CDCl_3$. [e] The solvent was $CDCl_3$.

Table III. 1-(Arylsulfonyl)methanesulfonamides (6)[a]

Ar	NR^1R^2	Yield, %	Mp, °C	—CH_2— chemical shift, δ[b]
4-$CH_3C_6H_4$	NH_2	84	179–181	5.100[c]
3,4-$Cl_2C_6H_3$	NH_2	90	179–181	4.933[c]
2,4,5-$Cl_3C_6H_2$	NH_2	90	218–220	...
C_6H_5	NHC_6H_5	50	151–153	5.349[c]
C_6H_5	$N(CH_3)_2$	90	102–103	...
4-$CH_3OC_6H_4$	$N(CH_3)_2$	77	110–112	4.546[d]
4-$(CH_3)_3CC_6H_4$		80	133–134.5	4.523[d]
C_6H_5		84	125–127	4.587[d]
C_6H_5		60	154–155	5.057[e]
4-ClC_6H_4		65	128–130	...

[a] Elemental analyses (for these compounds) in agreement with theoretical values were obtained and submitted for review. [b] Values are ±0.002 δ. [c] The solvent was DMSO–d_6. [d] The solvent was $CDCl_3$. [e] The solvent was acetone–d_6.



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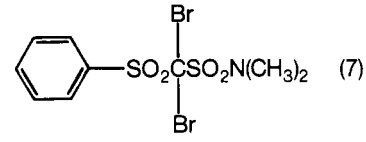

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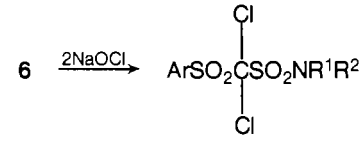
14

Chlorination of the sulfones (**6**) was easily effected with 5% sodium hypochlorite solution in aqueous dioxane (*2*) to give the corresponding 1-(arylsulfonyl)-1,1-dichloromethanesulfonamides (**15,** Equation 8, Table IV). Thus, **5** and **6** have been shown to behave as "active



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methylene" systems, readily undergoing halogenation under basic conditions.

Experimental

All melting points are uncorrected. Analyses were performed for carbon, hydrogen, nitrogen, sulfur, and halogens (where necessary) on all new compounds and agree, in all cases, with the theoretical values within ±0.3%. The elemental analyses were performed by the Michigan Division Analytical Laboratories of Dow Chemical U.S.A. The NMR spectral data reported in Tables II and III were obtained on a Varian A-60A spectrometer with tetramethylsilane as an internal standard. All of the compounds reported herein gave infrared and NMR spectra in agreement with their assigned structures.

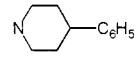
***1-Bromomethanesulfonamides* (*3*).** A solution of 26 g (0.25 mol) of triethylamine and 0.25 mol of the appropriate primary or secondary amine in 400 ml of dichloromethane was cooled to 1°, and a solution of 50 g (0.26 mol) of bromomethanesulfonyl chloride in 50 ml of dichloromethane was added dropwise, with stirring, while maintaining the temperature below 4°. The reaction mixture was then stirred at 25° for 19 h. The resulting precipitate was dissolved in 300 ml of water, and the organic layer separated and dried over anhydrous sodium sulfate. The dichloromethane was removed in vacuo, leaving the crude amide which was recrystallized from benzene/hexane or ethanol (Table I).

***1-(Arylthio)methanesulfonamides* (*5*).** To a solution of 4.6 g (0.20 g atm) of sodium in 500 ml of methanol was added 0.20 mol of arylthiol with stirring. To the resulting solution 0.10 mol of 1-bromomethanesulfonamide was added, and the solution was refluxed for 13 h. The solvent was removed in vacuo, and the residue treated with 250 ml of water. The product was filtered off, dried, and recrystallized from benzene/hexane or ethanol (Table II).

***1-(Arylsulfonyl)methanesulfonamides* (*6*).** To a solution of 0.044 mol of **5** in 43 ml of glacial acetic acid were added 15 ml of 30% hydrogen peroxide. The solution was heated at reflux for 1 h and then allowed to cool. The solution was poured into ice water, and the sulfone separated. The sulfone was filtered off, air dried, and recrystallized from ethanol (Table III).

***1-[(4-Methylphenyl)sulfinyl]methanesulfonamide* (*9*).** In a 100-ml, single-neck flask equipped with a magnetic stirrer were placed 0.40 g (0.84 mmol) of **7** and 30 ml of glacial

Table IV. 1-(Arylsulfonyl)-1,1-dichloromethanesulfonamides (15)[a]

Ar	NR^1R^2	Yield, %	Mp, °C
$4\text{-}CH_3C_6H_4$	NH_2	46	181–183
$3,4\text{-}Cl_2C_6H_3$	NH_2	48	125–128
$2,4,5\text{-}Cl_3C_6H_2$	NH_2	77	170–172
$4\text{-}CH_3OC_6H_4$	$N(CH_3)_2$	60	145–147
$4\text{-}(CH_3)_3CC_6H_4$		79	203–205
C_6H_5		95	185–187
$4\text{-}ClC_6H_4$		69	163–165

[a] Elemental analyses (for these compounds) in agreement with theoretical values were obtained and submitted for review.

acetic acid. To this solution, 0.08 g of 30% hydrogen peroxide was added, and the reaction mixture was heated to 65°. Examination of the acetic acid solution by NMR after several hours indicated that **9** was beginning to form (an AB quartet centered ca. 0.2 ppm downfield from the methylene signal of **7** began to appear). The reaction was continued for a total of 25 h with frequent monitoring by NMR. Additional 30% hydrogen peroxide was added in small amounts during this period, with a total of 0.30 g being added. After the 25-h reaction period, the reaction mixture was filtered and allowed to cool. Fine, white crystals formed which were filtered off, washed with ether, and dried to give 0.25 g (58% yield) of **9,** mp 215–217°.

1-[(3,4-Dichlorophenyl)sulfinyl]methanesulfonamide (10). To 0.50 g (1.84 mmol) of **8** in 25 ml of glacial acetic acid was added 0.10 g of 30% hydrogen peroxide. The reaction mixture was heated in an oil bath at 65°. Over a period of 7 h, an additional 0.37 g of 30% hydrogen peroxide was added in small increments, and the progress of the reaction was followed by NMR. After a 7-h reaction period, the acetic acid solution was filtered and allowed to cool. White crystals formed which were filtered, washed with ether, and dried to give 0.37 g (70% yield) of **10,** mp 205–207°.

1,1-Dibromo-N,N-dimethyl-1-(phenylthio)methanesulfonamide (12). To a solution of 1.0 g (4.32 mmol) of **11** and 0.68 g of pyridine in 15 ml of carbon tetrachloride was added a solution of 1.38 g (8.64 mmol) of bromine in 10 ml of carbon tetrachloride. After stirring for 2 h, NMR analysis of the reaction mixture showed 15% of **12,** 54% 1-bromo-*N,N*-dimethyl-1-(phenylthio)methanesulfonamide, and 31% unreacted **11.** An additional 0.5 g of bromine in 5 ml of carbon tetrachloride was added, and stirring continued for 15 h, after which an additional 1.5 g of bromine and 1.0 g of pyridine were added. After stirring for an additional 2 h, NMR analysis indicated 80% **12** and 20% 1-bromo-*N,N*-dimethyl-1-(phenylthio)methanesulfonamide. The reaction mixture was filtered, and the resulting filtrate cooled to give 0.78 g (48% yield) of **12** as white needles, mp 128–129°.

1,1-Dibromo-N,N-dimethyl-1-(phenylsulfonyl) methanesulfonamide (14). A 150-ml portion of a solution of 11.0 g of sodium hydroxide in 250 ml of water was added to 8.0 g (0.03 mol) of **13.** To the remaining sodium hydroxide solution were added 14.0 g (0.087 mol) of bromine, and the resulting solution was added dropwise to the sulfone slurry with stirring. After 30 min the crude dibromosulfone was filtered off, air dried, and recrystallized from ethanol to give 12.0 g (84% yield) of **14** as white crystals, mp 144–145°.

1-(Arylsulfonyl)-1,1-dichloromethanesulfonamides (15). A procedure which we have described previously (*2*) was employed for the preparation of these compounds (Table IV).

Acknowledgment

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