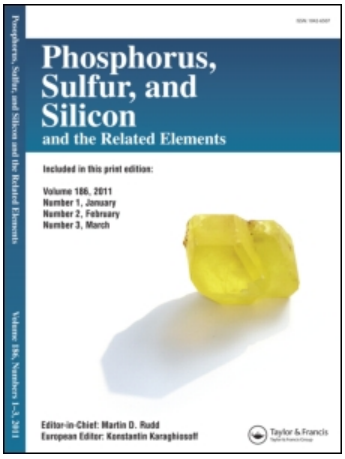

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SULFENAMIDES AND SULFINAMIDES X OXIDATION OF THIOLS BY ARYL SULFINAMIDES

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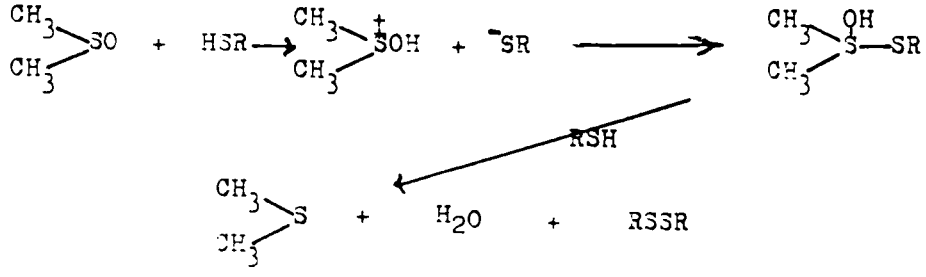
A dissection has been made of the oxidation of thiols by aryl sulfinamides, with the process explained by initial protonation of the sulfinyl group followed by a series of nucleophilic displacements, the first of which gives thiosulfinate and elimination of amine. The more usual reaction with thiosulfinate then gives disulfide, and sulfenic acid as a transitory intermediate, which by reaction with a third mole of thiol yields more disulfide. Reactions with lesser amounts of thiol permitted identification of intermediates. The effect of activation of the thiol is discussed. In contrast with oxidations by simpler sulfoxides the reaction proceeds without acid catalysis at ambient temperature, confirming the susceptibility to fission of the S—N bond in polar reactions.

Key words: Sulfinamide, sulfenamide, thiol, fission, nucleophilic displacement, disulfide.

INTRODUCTION

Extensive studies have shown that the extent and mode of participation of the sulfinyl group in a reaction are dependent on molecular structure and conditions employed. Frequently oxidations, as of iodide or thiols, have included acid whose role has been described as 'catalytic' in providing initial protonation of the sulfinyl group, although further participation has been noted on occasion with observations up to second order involvement.[1,2] The oxidation of thiols by sulfoxides has been studied in some detail[3] leading to a generally accepted mechanism in which a key step is a rate determining nucleophilic attack by a sulfenyl anion at the sulfur atom of the protonated substrate.



However, oxidations of thiols can proceed without added acid at a rate dependent on the acidity of the thiol. Relative rates of oxidations by tetramethylene sulfoxide have been reported in the order—thiophenol > 2-methylthiophenol > toluenethiol > 1-dodecanethiol—with suggestions of a linear relationship, possibly fortuitous, between activation energy and pKa value of each thiol.[4,5] Oxidations of thiols by heating at 80–90° in dimethyl sulfoxide, which functions as solvent and oxidizing

agent, have been described as an elegant method for the preparation of disulfides.[6] An earlier application to amino acid derivatives, oxidation of cysteine by methionine sulfoxide,[7] has been followed by observations of asymmetric reduction of several sulfoxides by L-cysteine.[8]

The present study extends the environment of the sulfinyl group to that of an acid amide in which it is possible to envisage several courses of reaction with thiols. First a simple redox reaction giving disulfide and sulfenamide then followed by nucleophilic displacement on sulfenamide giving more disulfide and amine. Alternatives are nucleophilic displacement at the sulfinyl group giving thiosulfinate and amine or a less like displacement giving sulfenamide and transitory sulfenic acid. Thiosulfinate and sulfenic acid then became intermediates competing for reaction with thiol.

Thus at the first step the competing possibilities are direct oxidation of the thiol, as with sulfoxides, and nucleophilic fission of the S—N bond.

RESULTS AND DISCUSSION

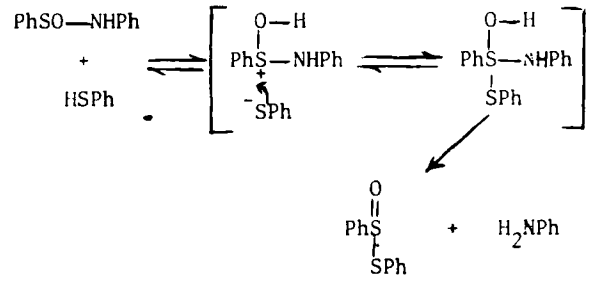
In ethanol the reaction of aromatic derivatives of thiols and sulfinamides proceeds readily at room temperature without acid catalysis, but the distribution of products is dependent on the molar ratio of reactants employed and on the activation of the thiol (Table I).

Table I, following exploratory reactions using a deficiency of thiol, results from the expectation that recognition of intermediates useful for determination of the course of reaction, would depend on small differences in rates of reaction with the thiol. Changes in the distribution of products as the proportion of thiol is increased make possible presentation of a reaction sequence.

TABLE I

Distribution of products from reaction of *N*-phenylbenzenesulfinamide with thiophenol

Sulfinamide/thiol molar ratio	1:1		1:2	1:3
Product (M)	8hr	16hr	16hr	16hr
Aniline	0.81	1.0	0.91	0.86
Phenyl disulfide (PhS.SPh)	0.44	0.43	0.91	0.86
Phenyl benzenethiosulfinate (PhSO.SPh)	0.40	0.17	-	-
Phenyl benzenethiosulfonate ($PhSO_2$.SPh)	0.04	0.22	0.08	-
Aniline benzenesulfinate ($PhSO_2^-$. H_3N^+Ph)	0.01	0	0.015	0.14
Recovery % M per M thiophenol				
C_6H_5NH	81	100	92	100
C_6H_5S	92	82	92	88



SCHEME 1

The first step, protonation of the sulfinyl group, is followed by a nucleophilic displacement involving fission of the S—N bond with an assisting elimination of amine and importantly retention of the sulfinyl group with formation of thiosulfinate.

Table I showing that irrespective of the course of reaction a sulfinamide/thiol reactant ratio of 1:3 would be required for complete reaction, also shows that with a reactant ratio as low as 1:1 an almost stoichiometric yield of amine was obtained with the sulfur moiety distributed between thiosulfinate and disulfide for a considerable time. The small yield of thiosulfonate may be attributed to decompositions probably of thiosulfinate in this medium. Scheme 1 is interesting when compared with fissions effected by attack of a sulfenyl anion on aromatic compounds featuring a disulfide (S—S), thiosulfinate (SO—S) or thiosulfonate (SO_2—S) group. In an unsymmetrical disulfide (S—S) attack occurs at the sulfur atom subject to greater electron withdrawing influences, as by a nitro group, but in the other derivatives the attack, contrary to a nominal expectation of occurrence at the oxidized sulfur as a result of electron withdrawing effects of the oxygen atom, nevertheless occurs at the sulfenyl sulfur as shown below. It has been shown that the rate of reaction at the oxidized sulfur is generally much slower.[9,10]

This preference is also in contrast with the action of aromatic thiosulfinates as inhibitors of vinyl polymerization where greater efficiency results from electron donation from substituents to the sulfenyl sulfur.[11] Thus a site of higher electron density preferred for radical attack would not have been expected to be favored for a nucleophilic attack.

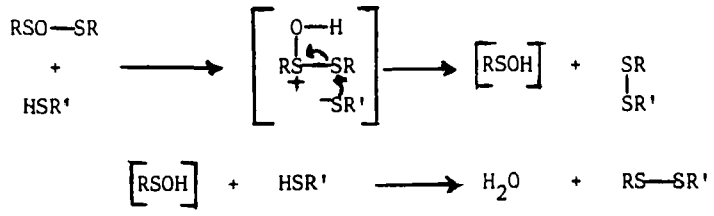
Formation of thiosulfinate rules out attack at the nitrogen since this would lead to sulfenamide which is not seen at any stage.

The next step, reaction of thiosulfinate with thiol giving disulfide, has been established as a very convenient method for the preparation of unsymmetrical disulfides since both sulfur atoms of the thiosulfinate appear in the product (Scheme 2).

The course of this reaction is interesting since a theoretical attack by a sulfenyl anion on a protonated sulfinyl group as in the first step would only give a mixture of thiosulfinates.

$$PhSO—SPh + HSR \rightleftharpoons PhSO—SR + HSPh$$

Extrusion of sulfenic acid as shown draws the reaction irreversibly to formation of disulfide.



SCHEME 2

In the early stages of the present reaction when, even with the 1:1 molar proportion of reactants, the availability of thiol is greater the secondary reaction proceeds to a limited extent so that some disulfide is formed. An accounting of yields with a sulfinamide/thiol ratio 1/1.25, may be made in the following terms. The first step requires an equimolar proportion of reactants so that the yield of aniline after 8 hr (0.8 M) implies that 0.8 M of thiosulfinate would be formed. But only 0.4 M was found hence the further implication that 0.45 M of thiol was used in reacting with thiosulfinate. Since the thiosulfinate/thiol reaction proceeds with a 1:2 stoichiometry formation of disulfide is reduced to 0.44 M and excess thiosulfinate is left in the product mixture. Times for the appearances of products using a deficiency of thiol are shown in Table II.

Thin layer chromatography showed that sulfinamide was present up to 3 hr but aniline and disulfide were detectable within 5 min. Appearance of thiosulfinate required longer since it seems to survive only as the availability of thiol declines.

Evidence supporting the proposed course of reaction was obtained using unsymmetrical systems—alternately substituting the sulfinamide or thiol with a methyl group (Table III).

TABLE II

Appearance of products from the reaction of *N*-phenylbenzenesulfinamide with thiophenol (1:1 molar ratio)

Product	Time for Identification			
	5min	3hr	4hr	8hr
Sulfinamide (reactant)	+	+	-	-
Phenyl benzenesulfenamide $C_6H_5S.NH\ C_6H_5$	-	-	-	-
Aniline	+	+	+	+
Diphenyl disulfide $C_6H_5S.SC_6H_5$	+	+	+	+
Phenyl benzenethiosulfinate $C_6H_5SO.SC_6H_5$	-	+	+	+
Phenyl benzenethiosulfonate $C_6H_5SO_2SC_6H_5$	-	-	-	+

TABLE III

Appearances of products from reactions of sulfinamides with thiols (1:1 molar ratio)

Product	Time for identification					
	5min		1hr		8hr	
	A	B	A	B	A	B
Aniline or p-Toluidine	+	+	+	+	+	+
Diphenyl disulfide (PhS.SPh)	-	+	-	+	-	+
p-Methyl diphenyldisulfide ($C_6H_5S.SC_6H_4CH_3$)	+	+	+	+	+	+
Di-p-Methylphenyl disulfide ($CH_3C_6H_4S.SC_6H_4CH_3$)	+	-	+	-	+	-
Phenylbenzenethiosulfinate ($C_6H_5SO.SC_6H_5$)	-	-	+	-	+	-
Unsymmetrical thiosulfinates ($C_6H_5SO.SC_6H_4CH_3$ $CH_3C_6H_4SO.SC_6H_5$)	-	-	-	+	-	+
Phenylbenzenethiosulfonate ($C_6H_5SO_2.SC_6H_5$)	-	-	-	+	-	+
Unsymmetrical thiosulfonates ($C_6H_5SO_2.SC_6H_4CH_3$ $CH_3C_6H_4SO_2.SC_6H_5$)	-	-	-	-	+	+

A *N*-Phenyl benzenesulfinamide with *p*-methylthiophenol.
B *N*-Phenyl-*p*-methylbenzenesulfinamide with thiophenol.

Rapid appearances of amine and a mixture of disulfides characterized both reactions. As required by Scheme 1, from reaction A both symmetrical di-*p*-methylphenyl disulfide and unsymmetrical mono-methyl disulfide were formed with the unsymmetrical disulfide containing the sulfur atom of the sulfinamide.

The equivalent trend was shown in reaction B where the same unsymmetrical disulfide was formed.

According to the sequence only unsymmetrical thiosulfinates should be formed. A problem therefore arises regarding the origin of symmetrical thiosulfinate formed at later stages, since it requires a source of disubstituted sulfur from the original sulfinyl group. In this event recourse is necessary to an exchange reaction between initially formed unsymmetrical thiosulfinate and disulfide. For the reactants in A this would be $C_6H_5SO \cdot SC_6H_4CH_3 + C_6H_5S \cdot SC_6H_4CH_3 \rightarrow C_6H_5SO \cdot SC_6H_5 + CH_3C_6H_4S \cdot SC_6H_4CH_3$.

With the aim of determining whether activation of the thiol would overcome differences in reaction rates of a sulfinamide and thiosulfinate, the reaction of *N*-phenylbenzenesulfinamide with *p*-nitrothiophenol was studied. The reaction was complete in 5 hr with both symmetrical and unsymmetrical disulfides appearing as rapidly as aniline—within 5 min (Table IV).

TABLE IV

Distribution of products[a] from the reaction of *N*-phenylbenzenesulfinamide with *p*-nitrothiophenol

	Molar ratio	
	1:1	1:2
Sulfinamide	0.54	—
Aniline	0.26	0.96
Di-*p*-nitrodiphenyl disulfide ($NO_2C_6H_4S \cdot SC_6H_4NO_2$)	0.44	0.76
p-Nitrodiphenyl disulfide ($C_6H_5S \cdot SC_6H_4NO_2$)	0.11	0.40
Diphenyl disulfide ($C_6H_5S \cdot SC_6H_5$)	tr	0.24

[a]Yield mole per mole *p*-nitrothiophenol.
Traces only of thiosulfinate and thiosulfonates.

Thiosulfinate was also detectable in trace amounts more quickly. The presence of residual sulfinamide with only a trace of thiosulfinate from the reactant mixture but absent from the 1:2 reaction is important to demonstration of the influence of the nitro group, shown at two points—in the first step and then in a faster reaction with intermediate thiosulfinates. The result is that production of disulfides is greater and yields of oxygenated derivatives lower. It is clear that the more active nitro derivative does not permit any accumulation of thiosulfinate. Any selectivity shown in substrate attack shown with thiophenol itself or its *p*-methyl derivative is overcome with the *p*-nitro derivative.

Synthesis of optically active thiosulfinates with predominantly inverted configuration and with stereospecificity varying from 30% to 80% has been observed from a series of *N,N*-dialkyl-*p*-tolylsulfinamides reacting with alkyl thiols.[12] The method used excess thiol in the presence of 2 molar equivalents of trichloroacetic acid, described as a catalyst. A mechanism, indirectly indicating the need for this quantity of acid proposed protonation of both sulfinyl group and amide nitrogen of the sulfinamide.

In contrast, identification of thiosulfinate as an intermediate in the present series is achieved without a catalyst and with its survival dependent on the molar proportion of thiol used. As this is increased the thiosulfinate yield declines until with 3 M proportion none survives. The differences in control of reaction may be discussed as follows.

At least a duofold role is proposed for the acid catalyst. In the medium, approximating a melt, the availability of sulfenyl anion as a displacing agent must be minimal. Formation of thiosulfinate with departure of the amine must be assisted if not primarily motivated by charge repulsion effects resulting from protonation of both functional groups of the sulfinamide. The repression of ionization of the thiol probably contributes to blocking the second step again requiring sulfenyl ion attack on the thiosulfinate but no longer assisted by charge repulsion effects.

The greater acidity of aromatic thiols allows protonation of the sulfinamide without need for acid. At the same time the availability of the anion leads to a competing reaction with thiosulfinate. Since *p*-nitrothiophenol provided a much faster acting aryl reagent it seems possible that conversion of thiosulfinate to di-

sulfide with alkyl thiols would be a slow process even in the absence of acid. It should be noted that in acetic acid reaction of the sulfinyl group of aryl thiosulfinates and sulfinamides with iodide proceeds very rapidly with sulfenamide proposed as the first product of reaction.[13]

EXPERIMENTAL

Sulfenamides and sulfinamides, prepared by condensation of a sulfenyl or sulfinyl chloride with the required amine as previously described in this series,[14] were recrystallized to satisfactory elementary analysis, melting point and single spot on chromatogram. Thiosulfinates and thiosulfonates and other reference compounds were prepared by standard methods. Unsymmetrical disulfides were prepared by the thiosulfinate/thiol reaction as illustrated by the preparation of *p*-nitrodiphenyl disulfide.

To a solution of *p*-nitrothiophenol (1.6 g, 0.01 M) in chloroform (15 ml) was added with stirring a solution of phenyl benzenethiosulfinate (1.2 g, 0.005 M in chloroform (15 ml). Solvent was removed *in vacuo*. The crude material (2.7 g, 100%) recrystallized from *n*-hexane gave fine yellow needles of *p*-nitrodiphenyl disulfide (Mp 56–57°, lit.[15] 58–58.5°).

(Found: C, 54.8; H, 3.5; N, 5.6; S, 24.25. Calc for $C_{12}H_9O_2NS_2$: C, 54.75; H, 3.4; N, 5; S, 24.3)

Aniline benzenesulfonate, prepared from its components had mp. 238°.
(Found: C, 57.15; H, 5.31; N, 5.67. Calc for $C_{12}H_{13}O_3NS$: C, 57.37; H, 5.18; N, 5.58)

Amine benzenesulfinate salts were prepared in a similar manner from benzenesulfinic acid and the appropriate amine.[16] Sulfinic acid was prepared by the reduction of sulfonyl chloride with sodium sulfite.[17]

Thin layer chromatography was performed using two systems:

1. On kieselguhr G plates impregnated with a solution (3% v/v) of phenoxyethanol in acetone and developed with *n*-hexane saturated with phenoxyethanol.
2. On kieselguhr G plates impregnated with a solution of liquid paraffin (3% v/v) in light petroleum and developed with methanol/water 70:30. Infrared measurements were made on Perkin Elmer 337 and 137 instruments.

Estimations of Products: Following upon qualitative testing which showed residual sulfinamide even after 2 hr using a sulfinamide/thiol molar ratio 1:1.25 products from a reaction using a 1:1 molar ratio and with reaction time increased, were estimated as follows.

N-Phenyl benzenesulfinamide (1.08 g, 5×10^{-3} M) in chloroform (25 ml) was added to a solution of thiophenol (0.55 g, 5×10^{-3} M) in chloroform (25 ml) and the mixture allowed to stand in the dark for 16 hr. Solvent was removed *in vacuo* at ambient temperature and replaced with ether (25 ml). After filtering off the small amount of undissolved aniline benzenesulfinate, the solution was washed with 0.5 M hydrochloric acid (50 ml) then with water (2×10 ml).

Evaporation of the acid extract to dryness gave a residue of aniline hydrochloride (0.59 g, 4.6×10^{-3} M) with infrared spectrum and that of its acetyl derivative (mp. 110° not depressed on admixture with acetanilide)† identical with reference material.

Removal of solvent from the ether solution gave a residue (0.5 g) to which was added a minimum amount of chloroform for solution then light petroleum to produce a slightly turbid solution. Cooling to −10° gave yellow crystals of phenylbenzenethiosulfinate (mp. 60°) and with the same R_f value by tlc on system 1 as reference material.

The residue obtained by removal of solvent from the filtrate, redissolved in carbon tetrachloride (25 ml) was chromatographed on a column of silica gel first with carbon tetrachloride (150 ml) to give diphenyl disulfide (0.212 g) mp. 58° and with R_f value by tlc on system 2 same as reference material. Further development of the column with chloroform (100 ml) gave phenylbenzenethiosulfonate mp. 35° and with infrared spectrum and R_f value by tlc on system 1 identical with reference material.

Thiosulfinate and thiosulfonate in the residue from the first ether extraction were estimated by the previously described methods.[18]

Thiosulfinate: To a portion of the residue in deaerated acetic acid (15 ml) was added a saturated solution of potassium iodide (2 ml). Liberated iodine required 0.01 M sodium thiosulfate 8.0 ml = 0.0187 g thiosulfinate.

†Mp's of all products performed also by admixture with reference material.

Thiosulfonate: To a portion of the residue (0.1206 g) in neutralized ethanol was added 20% v/v ethanolic solution of thiophenol (1 ml). Benzenesulfinic acid formed required 0.025 M sodium hydroxide, 4.6 ml = 0.0251 g of thiosulfonate. Identity of the thiosulfonate was confirmed by reacting with thiophenol as described then with aniline to obtain aniline benzenesulfinate mp. 131° and with infrared spectrum identical with that of reference material. Tables I and II present results from these estimations corrected for the total recovery.

Reactions of *N*-phenylbenzenesulfinamide with *p*-methylthiophenol and of *N*-*p*-methylphenylbenzenesulfinamide with thiophenol in each case using 1:1 molar proportions were performed in a similar manner. Results are shown in Table III.

Reaction of *N*-phenylbenzenesulfinamide with *p*-nitrothiophenol. The progress and products from this reaction are shown in Table IV.

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