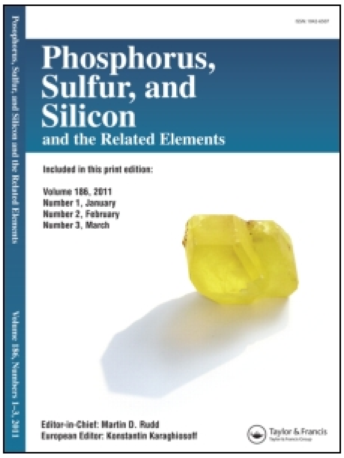

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α-(METHYLTHIO)BENZYL SULFONES AS SYNTHETIC INTERMEDIATES. PART IV.[1] SOME NEW *o*-, *m*- AND *p* -SUBSTITUTED α-(METHYLTHIO)- AND α,α'-BIS- (METHYLTHIO)-BENZYL SULFONES

B. Wladislaw[a]; L. Marzorati[a]; G. Ebeling[a]
[a] Instituto de Química, Universidade de Sãto Paulo, Sãto Paulo, S. P., Brazil

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α-(METHYLTHIO)BENZYL SULFONES AS SYNTHETIC INTERMEDIATES. PART IV.[1]
SOME NEW *o*-, *m*- AND *p*-SUBSTITUTED α-(METHYLTHIO)- AND α,α′-BIS-(METHYLTHIO)-BENZYL SULFONES

B. WLADISLAW,† L. MARZORATI and G. EBELING
Instituto de Química, Universidade de São Paulo, Caixa Postal 20.780, São Paulo – S.P., Brazil

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The reaction of the meta nitro, methoxy and cyano substituted benzylic sulfones with an excess of dimethyl disulfide, in the presence of NaH/DMSO, affords the corresponding α-monosulfenylated derivatives. However, no reaction occurs with the corresponding *o*-substituted sulfones. A new procedure is developed using *S*-methyl methanethiosulfonate, in excess, in the "phase transfer condition" which lead for the *o*-nitro and *o*-methoxy substituted sulfones to the α-monosulfenylated derivatives and for the *o*-cyano as well as *p*- and *m*-nitro, *m*-methoxy and *m*-cyano substituted benzylic sulfones to the corresponding α,α′-bis-sulfenylated derivatives.

Key words: Sulfones; monosulfenylation; bis-sulfenylation; dimethyl disulfide; *S*-methyl methanethiosulfonate.

INTRODUCTION

The *p*-substituted α-(methylthio)benzyl sulfones showed to be useful intermediates for the syntheses of the *p*-substituted benzaldehydes,[2] 1-deuterobenzaldehydes[3] and phenyl alkyl ketones.[1] The preparation of these intermediates by sulfenylation of the corresponding benzylic sulfones using an excess of dimethyl disulfide and NaH/DMSO has been reported.[2]

It was of interest to synthesize the *m*- and *o*-substituted α-(methylthio)benzyl sulfones, potential intermediates for the syntheses of the *m*- and *o*-substituted aromatic aldehydes and ketones. Therefore, the sulfenylation study of the corresponding benzylic sulfones was undertaken.

RESULTS AND DISCUSSION

The results are shown in Table I. It may be seen that when some *m*-substituted benzylic sulfones (**1a–c**) were treated with an excess of dimethyl disulfide and NaH/DMSO the expected α-methylthio derivatives (**2a–c**) were obtained. However, the corresponding *o*-substituted benzylic sulfones (**3a–c**) showed to be

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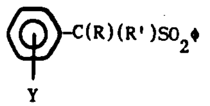
† Author to whom all correspondence should be addressed.

TABLE I

Sulfenylation reactions

Starting sulfones				Products							
 Y= NO_2(a), OMe(b), CN(c), H(d)				MeSSMe (excess)/ NaH/DMSO				MeSSO$_2$Me (excess)/ NaOH/ϕH/2HT75			
Position of *Y*	Cpd	R	R′	Cpd	R	R′	Yield %	Cpd	R	R′	Yield %
meta	**1a**	H	H	**2a**	H	SMe	73	**6a**	SMe	SMe	90
	b	H	H	**b**	H	SMe	57	**b**	SMe	SMe	45
	c	H	H	**c**	H	SMe	54	**c**	SMe	SMe	71
ortho	**3a**	H	H		no reaction			**4a**	H	SMe	82
	b	H	H		no reaction			**b**	H	SMe	65
	c	H	H		no reaction			**c**	H	SMe	71[a]
								5c	SMe	SMe	50
para	**7a**	H	H		(see ref. 2)			**8a**	SMe	SMe	66
	d	H	H		(see ref. 2)			**d**	SMe	SMe	71

[a] MeSSO$_2$Me (1:1)/NaH/DMSO.

unreactive toward the same reagent. Nevertheless, they underwent sulfenylation reaction when treated with an excess of *S*-methyl methanethiosulfonate, under the "phase transfer condition", leading, in the case of the *o*-nitro and *o*-methoxy substituted benzyl sulfones (**3a, b**), to the corresponding monosulfenylated derivatives (**4a, b**) and in the case of the *o*-cyano substituted benzylic sulfone (**3c**) to the corresponding α,α'-bis-sulfenylated derivative (**5c**). When this new procedure of sulfenylation was applied to three *m*-substituted (**1a–c**), to *p*-nitrosubstituted (**7a**) and to unsubstituted (**7d**) benzylic sulfones, the corresponding α,α'-bis-sulfenylated derivatives (**6a–c**) and (**8a, d**) were obtained.

However, it was possible to obtain the *o*-cyano substituted α-monosulfenylated derivative (**4c**) using thiosulfonate (1:1) in the presence of an excess of NaH/DMSO.

The fact that the *o*-substituted benzylic sulfones did not react with an excess of dimethyl disulfide, in contrast to the corresponding *p*- and *m*-derivatives, which undergo monosulfenylation, cannot be attributed to electronic effects of the substituents, but is, most probably, due to steric hindrance. Similar explanation can be given for the difference in reactivity toward a more powerful reagent-*S*-methyl methanethiosulfonate-, which with *p*- and *m*-nitro and *m*-methoxy derivatives give bis-sulfenylated products, but with the corresponding *o*-derivatives afford monosulfenylated products. The exceptional case of the *o*-cyano benzylic sulfone, which behaves similarly to the corresponding *p*- and *m*-derivatives to undergo bis-sulfenylation when treated with *S*-methyl methanethiosulfonate, may be attributed to the unhindered linear geometry of the cyano group.

The difference in reactivity shown by the *p*- and *m*-substituted sulfones toward dimethyl disulfide and *S*-methyl methanethiosufonate, both in excess, leading, respectively, to mono- and bis-sulfenylated derivatives, may be also rationalized. In analogy to the sulfenylation of ketones[4] and β-keto-sulfones[5] it may be suggested that in the case of the dimethyl disulfide the bis-sulfenylated product is also initially formed but it undergoes desulfenylation through an attack on sulfur by methylthio leaving group to give α-methylthio-carbanion, which survives in DMSO until quenched. It is probable that in the case of *S*-methyl methanethiosulfonate the corresponding leaving group is too hard a nucleophile to promote such desulfenylation.

Beside the α-(methylthio)benzyl sulfones, intermediates to the carbonyl compounds the new α,α′-bis-(methylthio)benzyl sulfones, thermally unstable,[6] are showing promise as useful intermediates for the syntheses of the ring substituted thiobenzoates.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Varian model T-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin–Elmer model 283 spectrophotometer. Melting points were determined on a Kofler hot stage apparatus and were uncorrected. Microanalyses were performed on a Perkin-Elmer 240 B elemental analyser.

All starting benzylic sulfones were prepared by oxidation of the corresponding sulfides with hydrogen peroxide in acetic acid[7] (see Table II). The sulfenylation reactions of benzylic sulfones (10 mmol) with NaH (20 mmol) and dimethyl disulfide (30 mmol) in DMSO (35 ml) were performed as described previously.[2]

Sulfenylation reaction with S-methyl methanethiosulfonate under phase transfer condition. General procedure. An aqueous solution of sodium hydroxide (50%, 15 ml) containing 0.10 g of Herquat 2HT75[8] (a mixture of dialkyl—75% C_{18}; 25% C_{16}-dimethylammonium chloride, "Herga Indústria Química", Rio de Janeiro, Brazil) is added to a suspension of benzyl phenyl sulfone (**1a–c**; **3a–c**; **7a–d**; 10 mmol) in benzene (10 ml). Then, a solution of *S*-methyl methanethiosulfonate (50 mmol) in benzene (20 ml) is added dropwise over a period of 5 hours, under continued stirring, at room

TABLE II

Some *o*-, *m*- and *p*-substituted benzylic sulfones[a]

Cpd.	Yield %	Mp(lit Mp) °C	^{1}H NMR ($CDCl_3$, δ)
1a	92	163–4(163)[b]	4.38(s, 2H); 7.25–8.42(m, 9H)
b	72	108–11[c]	3.65(s, 3H); 4.22(s, 2H); 6.45–7.75(m, 9H)
c	73	158–60(157–9)[d]	4.28(s, 2H); 7.30–7.85(m, 9H)
3a	95	112–3(113)[b]	5.00(s, 2H); 7.30–8.20(m, 9H)
b	90	79–80[e]	3.32(s, 3H); 4.37(s, 2H); 6.40–7.80(m, 9H)
c	87	152–4[f]	4.53(s, 2H); 7.30–7.90(m, 9H)
7a	85	204–5(204–5)[g]	4.57(s, 2H); 7.20(d, 2H, $J = 9$ Hz); 7.57(m, 5H); 8.08(d, 2H, $J = 9$ Hz)
d	91	144–6(144–5)[g]	4.23(s, 2H); 6.87–7.73(m, 10H)

[a] ν_{SO_2}(cm^{-1}) ca. 1155, 1310.
[b] J. Tröger and E. Nolte, *J. Prakt. Chem.*, 101, 136 (1920).
[c] From ethanol. Calcd. % C, 64.10; H, 5.38; found % C, 64.05; H, 5.36.
[d] B. B. Jarvis and J. C. Saukaitis, *J. Am. Chem. Soc.*, 95, 7708 (1973).
[e] From ethanol. Calcd. % C, 64.10; H, 5.38; found % C, 63.80; H, 5.36.
[f] From ethanol. Calcd. % C, 65.35; H, 4.31; N, 5.44; found % C, 65.24; H, 4.21; N, 5.57.
[g] See ref. 7.

TABLE III

Characterization of some new α-(methylthio)benzyl sulfones[a]

Cpd.	Mp(°C) Solvent	Formula m.w.	Analysis % calcd./found C	H	^{1}H NMR ($CDCl_3$/TMS) δ
2a	157–9	$C_{14}H_{13}O_4S_2N$	52.00	4.05	2.47(s, 3H); 4.93(s, 1H); 7.13–8.25(m, 9H)
	A	(323.4)	52.21	4.26	
2b	107–9	$C_{15}H_{16}O_3S_2$	58.42	5.23	2.47(s, 3H); 3.67(s, 3H); 4.77(s, 1H); 6.47–7.74(m, 9H)
	B	(308.4)	58.63	5.56	
2c	117–20	$C_{15}H_{13}NO_2S_2$	59.38	4.32	2.43(s, 3H); 4.80(s, 1H); 7.12–7.80(m, 9H)
	B	(303.4)	59.68	4.64	
4a	67–8	$C_{14}H_{13}NO_4S_2$	52.00	4.05	2.40(s, 3H); 6.05(s, 1H); 7.10–7.90(m, 9H)
	B	(323.4)	52.24	4.11	
4b	112–4	$C_{15}H_{16}O_3S_2$	58.42	5.23	2.48(s, 3H); 3.44(s, 3H); 5.30(s, 1H); 6.46–7.70(m, 9H)
	B	(308.4)	58.10	5.27	
4c	94–6	$C_{15}H_{13}NO_2S_2$	59.38	4.32	2.48(s, 3H); 5.18(s, 1H); 7.10–8.00(m, 9H)
	B	(303.4)	59.37	4.37	

[a] ν_{SO_2}(cm^{-1}) *ca.* 1144, 1305.

Key of solvent: A = ethanol/chloroform; B = methanol.

temperature. When the addition is completed, water is added (10 ml) and the aqueous layer is further extracted with benzene. The combined organic extract is washed 3 times with water (20 ml) containing sodium perchlorate (8 g) and 20% hydrochloride acid (4 ml), dried ($MgSO_4$), filtered through a short silica gel column (15 g; Merck 60) for removing the quartenary ammonium salt and evaporated in vacuo. The crude solid product is washed with cold methanol, filtered and recrystallized from the appropriate solvent (see Table III and IV).

Sulfenylation reaction of (**3c**) *with S-methyl methanethiosulfonate* (1:1) *in DMSO.* Compound **3c** (5 mmol) is added to a stirred suspension of sodium hydride (12 mmol, obtained from a 60% dispersion in mineral oil by washing with dry benzene) in dimethyl sulfoxide (10 ml), at room temperature, and stirring is continued for 30 minutes. The *S*-methyl methanethiosulfonate (5 mmol) is added and stirring is continued for 15 minutes. The mixture is poured into an aqueous solution of ammonium chloride (6%) and extracted with dichloromethane (3 × 10 ml). The organic extract is washed 3 times with water (50 ml) containing sodium chloride (5 g) and dried with anhydrous

TABLE IV

Characterization of some new α,α′-bis-(methylthio)benzyl sulfones

Cpd.	Mp(°C) Solvent	Formula m.w.	Analysis % calcd./found C	H	^{1}H NMR ($CDCl_3$/TMS) δ
5c	142–4	$C_{16}H_{15}NO_2S_3$	54.99	4.33	2.20(s, 6H); 7.15–8.40(m, 9H)
	A	(349.5)	54.99	4.36	
6a	116–8	$C_{15}H_{15}NO_4S_3$	48.76	4.09	2.27(s, 6H); 7.10–8.25(m, 9H)
	B	(396.5)	48.76	4.15	
6b	104.0–104.5	$C_{16}H_{18}O_3S_3$	54.21	5.12	2.27(s, 6H); 3.67(s, 3H); 6.60–7.90(m, 9H)
	A	(354.5)	54.19	5.47	
6c	122–4	$C_{16}H_{15}NO_2S_3$	54.99	4.33	2.25(s, 6H); 7.20–8.10(m, 9H)
	A	(349.5)	54.87	4.31	
8a[a]	113–4	$C_{15}H_{15}NO_4S_3$	48.76	4.09	2.27(s, 6H); 7.05–8.10(m, 9H)
	A	(369.5)	48.86	4.22	
8d	104–5	$C_{15}H_{16}O_2S_3$	55.52	4.97	2.25(s, 6H); 6.90–7.70(m, 10H)
	C	(324.5)	55.35	5.03	

[a] ν_{SO_2}(cm^{-1}) 1149, 1322.

Key of solvents: A = methanol; B = methanol/chloroform; C = hexane/chloroform.

magnesium sulfate. The solvent is removed and the crude soild product is crystallized by adding methanol. After recrystallization from methanol 71% of pure **4c** is obtained.

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