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ISOPRENE FUNCTIONALIZATION

E/Z-ISOMERISM OF 1-SULFONYL SUBSTITUTED 2-METHYLBUTADIENES

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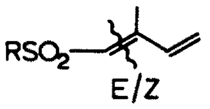
Abstract—The isomeric chlorosulfones 3, 4 and 5 are prepared by 1,4-addition of sulfonyl chlorides to isoprene, Dehydrohalogenation affords the corresponding 2- and 3-methylbutadienyl sulfones in a configuration which is dependent on the configuration of the chlorosulfone. Pure *Z*-2-methylbutadienyl sulfones 1 are obtained by displacement of primary halides by the *Z*-sulfinate anion 2. The *Z*-sulfones 1 are isomerized to *E/Z*-mixtures. The *E/Z*-mixtures are separated into their components and the configuration of the isomers is established by the NMR-NOE technique.

As isoprene synthons in the Michael induced Ramberg-Bäcklund (MIRB)[1] stepwise synthesis of conjugated isoprenoids, we required the *E*- and the *Z*-sulfones of general structure 1.



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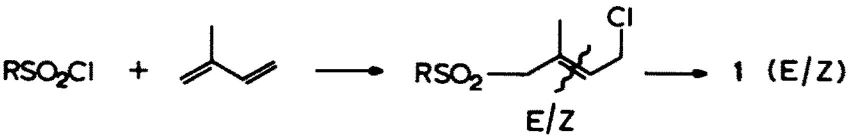
Two literature procedures for the conversion of isoprene into the title compounds appeared suitable for this purpose. The first method (eqn 1) utilizes the copper-(I)-catalyzed 1,4-addition of sulfonyl chlorides to isoprene[2], followed by dehydrohalogenation of the resulting chlorosulfones. This method is restricted to those groups R, that can be obtained as sulfonyl chloride. The second method (eqn 2) consists of the displacement of an activated (preferably allylic) halide by 2-methyl-1,3-butadienyl sulfinic anion 2, prepared by base treatment[a] of the isoprene/SO_2-adduct.[3] Several 1-sulfonyl substituted 2-methylbutadienes of unspecified stereochemistry have been reported in the literature. We have developed a method to establish the configuration. In contrast to the high stereoselectivity, claimed for the first method, the reaction resulted in the formation of configurational as well as positional isomers[b] in our hands. However, the *Z*-configuration of the potassio sulfinite 2, used in eqn (2), is retained throughout the substitution reaction, and high purity *Z*-sulfones 1 are obtained in this way.



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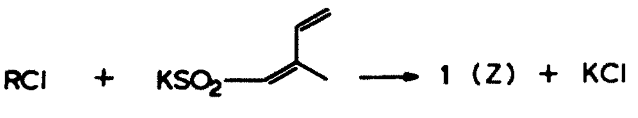

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(2)

Neither of the methods give direct acess to the pure *E*-sulfones 1. We have therefore increased the *E*-content of those mixtures, which contained a low percentage of the *E*-isomer, by the use of an isomerization catalyst. An *E/Z*-ratio of roughly 2 was observed for all sulfones studied. Separation of the isomers from their *E/Z*-mixtures proved to be difficult.

RESULTS AND DISCUSSION

Addition of sulfonyl chlorides to isoprene, eqn (1)

The addition of sulfonyl chlorides to isoprene, following the procedure described in the literature,[2] leads to mixtures of the isomeric chlorides 3, 4 and 5 (Table 1). The dehydrohalogenation of these mixtures resulted in methylbutadienylsulfone mixtures of constant composition, irrespective the nature of the groups R.

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[a] We have established the *Z*-configuration of the sulfinic acid salt, prepared in this manner, by the use of NMR-NOE technique.

[b] Conparable observations have been made by others.[4]

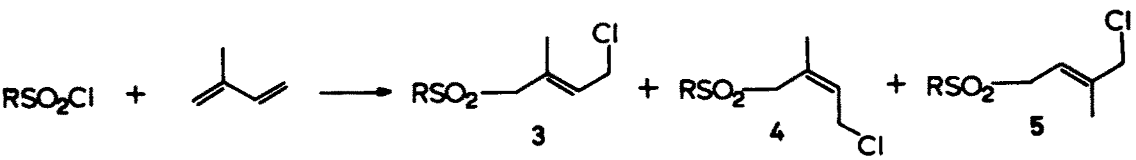


Table 1. Addition of sulfonyl chlorides to isoprene

R	Yield (%) 3,4+5	3+4(%)*	5(%)*
p-tolyl	82	79	21
phenyl	75	81	19
methyl	91	78	22
chloro methyl**	78	83	17

*Based on ^{1}H NMR of the mixtures. Because of signal overlap (see Table 2) the percentages of 3 and 4 can not be calculated separately.

**Prepared following ref. 1.

Table 3. Dehydrohalogenation of 3, 4 and 5 with 1 Eq of Et_3N in benzene

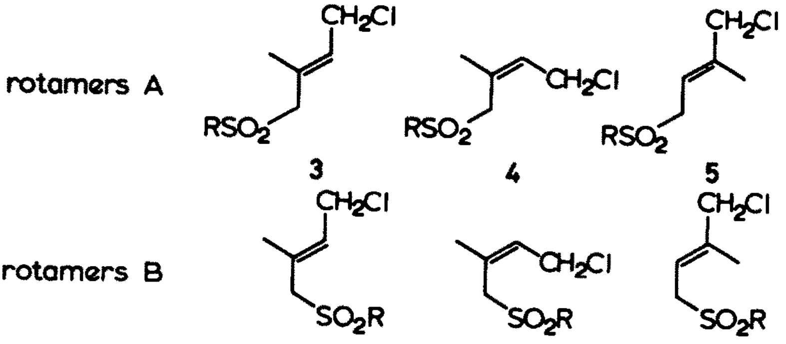
R	Conpound	Yield(%)	*Butadienyl sulfones** E-2-Me(%)	Z-2-Me(%)
p-tolyl	3	100	31	69
phenyl	3	79	33	67
methyl	3	80	32	68
p-tolyl	4	100	100	—
phenyl	4	100	100	—
methyl	4	50	100	—
			E-3-Me(%)	*Z*-3-Me(%)
p-tolyl	5	92	100	—

*Based on ^{1}H NMR.

In several cases we have isolated the isomers from the reaction mixtures by column chromatography. The stereochemistry around the double bond was established by NMR-NOE experiments. Table 2 contains the NMR-data.

1,4-*Elimination of* HCl *from* 3, 4 *and* 5

Treatment of benzene solutions of 3, 4 and 5, either as a mixture or in separate form, with one equivalent of triethylamine leads to a smooth dehydrohalogenation in almost quantitative yield. The stereochemical course of the elimination reactions (Table 3) can be understood by considering the various rotamers of the starting chlorosulfones, shown in Scheme 1. The rotamers A and B of isomer 3 resemble the transition states leading to the *E*- and *Z*-2-methylbutadienyl sulfones 1, respectively. Since the two rotamers have little difference in nonbonded interactions, the *E*-chloride 3 can be expected to give *E*/*Z*-mixtures of dienyl sulfones upon dehydrohalogenation. With the chlorosulfones 4 and 5, however, rotamer A is considerably less hindered than rotamer B. Consequently 4 and 5 will predominantly lead to the *E*-isomers of the 2- and 3-methylbutadienyl sulfones, respectively (Table 3). We have found no *E*/*Z*-isomerization takes place under the reaction conditions.



Scheme 1.

Table 2. ^{1}H NMR-data of 3, 4 and 5

R	Compound	Sulfonyl–CH_2	Methyl^a	Vinyl^a	Chloro–CH_2
p-tolyl	3	3.76(s)	1.85	5.38	3.98(d,J 8Hz)
	4	3.87(s)	1.85	5.80	3.80(d,J 8Hz)
	5	3.86(d,J 8Hz)	1.50	5.65	4.00(s)
phenyl	3	3.83(s)	1.88	5.41	4.01(d,J 8Hz)
	4^b	3.91(*s*)	1.87	5.83	3.83(*d,J* 8*Hz*)
	5^c	3.88(*d,J* 8*Hz*)	1.45	5.67	4.00(*s*)
methyl	3	3.78(s)	1.98	5.90	4.20(d,J 8Hz)
	4	3.90(s)	2.03	5.98	4.20(d,J 8Hz)
	5^d		1.92		

[a] Methyl-absorptions: broad s; vinyl-absorptions: t, J 8Hz.

[b] Prepared following ref. 5.

[c] Isolated as a chromatographic fraction, mixed with 61% of 3.

[d] Mixed with 3 and 4.

Synthesis of Z-sulfones 1 *by eqn* (2)

The displacement of primary halides by the sulfinate anion 2 was performed as described in the literature.[3] The halides having groups R, as specified in Table 4, were isolated as pure *Z*-sulfones 1. The ^{1}H NMR-data of the dienyl moiety of some of these sulfones are given in Table 5.

Configurational assignment of the sulfones 1.

The literature ^{1}H NMR-data, designed to estimate the chemical shifts of olefinic hydrogens using additive increments,[6] were insufficiently decisive to establish the configuration of the butadienyl sulfones 1. However, we have noted, that all sulfones 1, we have prepared, can be classified into two distinct groups, after the chemical shift of H_c (Table 5). NMR-NOE experiments showed, that the sulfones having a low-field H_c-absorption possess the *Z*-configuration. The NMR-data are listed in Table 5.

Z/E-Isomerization of Z-2-methyl-1,3-butadienyl sulfones 1

Sulfones 1 with an isoprenoid group R were only available to us by eqn (2)[a] and therefore have a *Z*-configuration of the butadienyl moiety. Attempted synthesis of the *E*-isomer, corresponding to the sulfinic acid salt 2, by the use of an isomerization catalyst was unsuccessful.

For this reason we have studied the *Z*/*E*-isomerization of the *Z*-sulfones 1, prepared by eqn (2).

Light induced isomerization was performed at various wave-lengths and in several solvents. An *E*/*Z*-ratio of 0.7 was observed, but the purification was hampered by polymerization products. All isomerizations of 1-sulfonyl substituted 2-methyl-butadienes 1 required considerably higher temperatures and catalyst concentrations than comparable literature procedures.[7,8]

A $PhSO_2H$-catalyzed isomerization in refluxing dioxane,[7] believed to proceed by the addition/elimination of phenyl sulfonyl radicals, leads to *E*/*Z*-mixtures of 1. The equilibrium mixture with an *E*/*Z*-ratio of 2 was attained after 18 hr with 0.8 equivalents of $PhSO_2H$. Purification of the *E*/*Z*-mixture was cumbersome because of the presence of decomposition products derived from the catalyst. However, refluxing a *n*-heptane solution of the *Z*-sulfones 1 with 0.1 equivalents of iodine[8] overnight, afforded the equilibrium mixture, without any decomposition.

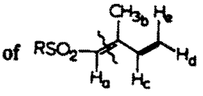
Separation of the isomers from E/Z-mixtures

From HPLCaobservations[b] on a mixture, consisting of 60% prenyl-*E*- and 40% prenyl - *Z* - 2 - methyl - 1, 3 - butadienyl sulfone (Fig. 1) it could be predicted, that the separation on a practical scale of the *E*- and *Z*-sulfones 1 from their mixtures would be difficult. When a mixture of sulfones 1 with an *E*/*Z*-ratio of 2 is dissolved at r.t. in ether/*n*-hexane, predominantly the *Z*-isomer crystallizes upon chilling to −20°C. In this way 65% of product, having an *E*/*Z*-ratio of 4.5, was recovered from the mother liquor. Any further enrichment provide impossible. The usual chromatographic separation techniques resulted in comparable *E*/*Z*-ratios when performed on a practical scale.

Table 4. Synthesis of *Z*-sulfones 1 in DMSO at room temperature

R	Yield (%)
prenyl	84
geranyl	97
β-cyclogeranyl	38
benzyl	81
methyl	29
3-methyl-*Z*-2-pentenyl	50
2-methyl-2-propenyl	70

Table 5. ^{1}H NMR-absorptions* of



R		H_a	H_b	H_c	H_d	H_e
prenyl	E†	6.06	2.13	6.27	5.37	5.59
	Z	5.99	1.96	7.50	5.46	5.58
geranyl	E†	6.11	2.20	6.31	5.43	5.64
	Z	6.02	1.98	7.57	5.49	5.61
α-cyclogeranyl	E†	6.20	2.24	6.34	5.45	5.66
	Z	6.17	2.03	7.65	5.57	5.67
benzyl	E†	6.02	1.87	6.27	5.42	5.58
	Z	5.94	1.98	7.27	5.40	5.56
p-tolyl‡	E	6.28	2.22	6.28	5.42	5.62
	Z	6.25	1.98	7.80	5.58	5.65
phenyl‡	E	6.38	2.27	6.40	5.48	5.68
	Z	6.27	1.98	—§	5.60	5.68
methyl‡	E	6.28	2.29	6.36	5.51	5.71
	Z	6.22	2.02	7.55	5.53	5.64
chloro methyl‡	E	6.21	2.33	6.43	5.58	5.79
	Z	6.13	2.12	7.58	5.64	5.76

*Apparent δ and J values; H_a, broad s; H_b, d, J 0.5HZ; H_c, X-part of ABX, J_{cd} 11Hz, J_{ce} 18Hz; H_d, A-part of ABX; H_e, B-part of ABX, J_{de} 0.5Hz.

†Prepared by isomerization as described in the following section.

‡Prepared by dehydrohalogenation following eqn (1).

§Overlapping with phenyl-absorptions (7.47 − 8.13 ppm).

Small quantities of prenyl- and benzyl-*E*-2-methyl-1, 3-butadienyl sulfones were obtained upon glc-separation on a SE-30 column with retention times of approximately 28 minutes.[c]

Larger quantities were prepared by the following procedure. An *E*/*Z*-sulfone mixture was treated with base at low temp. Only the *Z*-anion entered into an intramolecular 1, 4-addition. Acidification resulted in a mixture of the unconverted *E*-sulfone and the isomeric cyclized sulfone. Separation of this mixture provided no problems. Full details of this method will be published in a forthcoming communication.

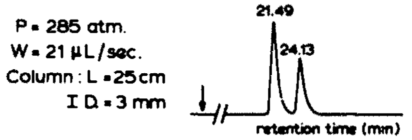


Fig. 1. HPLC-separation Si 60 (5–8μ) with 1% dioxane in *n*-hexane as eluens.

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[a] Attempted synthesis of the corresponding isoprenoid sulfonyl chlorides, required for eqn (1), failed in our hands.

[b] Dr. J. C. Kraak, Laboratory of Analytical Chemistry of our University.

[c] No thermal *E*/*Z*-isomerization was observed.

EXPERIMENTAL

Phenyl sulfinic acid was obtained by acidification with HCl of an aqueous soln of its Na salt. All reactions were performed under N_2. Chromatographic separations were carried out on pre-packed columns (Merck, Lobar, LiChroprep Si 60), using EtOAc/P.A. as an eluens at 2 atm pressure. ^1H NMR (TMS, $\delta = 0$, $CDCL_3$) was recorded on a Varian A 60 D and a Varian XL-100 NMR Spectrometer; IR on a Perkin Elmer model 177. M.ps were determined on a Leitz-Wetzlar apparatus and are uncorrected.

1, 4-*Addition of sulfonyl chlorides to isoprene*[a]

General procedure. A mixture of sulfonyl chloride (0.1 mole), isoprene (0.2 mole), cuprous chloride (1 mmole), triethylamine. HCl (1.5 mmole) and 5 ml of acetonitrile was refluxed for 18 hr. Work-up by the published procedure[9] afforded mixtures of the isomeric 3, 4 and 5 as indicated in Table 1. Pure samples of 3, 4 and 5 were obtained by chromatographic separation. ^1H NMR-data are given in Table 2.

Dehydrohalogenation of 3, 4 and 5

General procedure. Triethylamine (5.5 mmole) was added to a benzene soln (50 ml) of 3, 4 or 5 (5 mmole). After stirring for 4 days at r.t. the mixture was filtered and the benzene was removed *in vacuo*. The 2- and 3-methyl-1, 3-butadienyl sulfones (Table 3) were obtained as oils. ^1H NMR-data are given in Table 5[b].

Potassio Z-2-methyl-1, 3-butadienyl sulfinate 2

The *Z*-sulfinic salt[3] was obtained in 90% yield as a hygroscopic white powder. ^1H NMR (d_6-DMSO): 7.25(C3–H, X-part of ABX, J_{AX} 11 Hz, J_{BX} 18 Hz); 5.78(C1–H, broad s); 5.17(C4–H, B-part of ABX, J_{AB} 0.5 Hz); 5.10(C4–H, A-part of ABX); 1.73(CH_3, d, J 0.5 Hz).

Synthesis of Z-2-methyl-1, 3-butadienyl sulfones 1 by eqn (2)

General procedure. The primary halide (105 mmole; Table 4) in dry DMSO (50 ml) was added to a DMSO soln (100 ml) of the *Z*-sulfinic salt 2 (100 mmole) at r.t. After stirring for 40 hr the DMSO was removed *in vacuo*. Chromatographic purification of the oily residue afforded the *Z* - 2 - methyl - 1, 3 - butadienyl sulfones 1, as indicated in Table 4. ^1H NMR-data are given in Table 5.

Prenyl-*Z*-2-methyl-1, 3-butadienyl sulfone was obtained in a colourless crystalline form (m.p. 77.5–78.5°). IR($CHCl_3$): 1660, 1620, 1570 (C=C), 1310, 1280 and 1110 cm^{-1} (SO_2). (Found: C, 60.03; H, 7.89; S, 15.89. Calcd for $C_{10}H_{16}SO_2$: C, 59.96; H, 8.05; S, 16.01; O, 15.98).

Benzyl-*Z*-2-methyl-1, 3-butadienyl sulfone; m.p. 82–83°. IR($CHCl_3$): 1615 (C=C), 1560, 1490 (phenyl), 1300, 1280, 1120, 1100 cm^{-1}(SO_2). (Found: C, 64.95; H, 6.29; S, 14.57; O, 14.59. Calcd for $C_{12}H_{14}SO_2$: C, 64.83; H, 6.35; S, 14.42; O, 14.40).

The other *Z*-sulfones 1 (Table 4) were obtained in a liquid form.

Z/E-*Isomerization of the* Z - 2 - *methyl* - 1, 3 - *butadienyl sulfones* 1

General procedure. *Z*-sulfone 1 (20 mmole) was added to a warm soln of iodine (2 mmole) in $CHCl_3$ (10 ml)/dry n-heptane (800 ml). The mixture was refluxed for 40 hr. The iodine was removed by two washings with $Na_2S_2O_3$ soln. The washings were extracted with $CHCl_3$. The combined n-heptane and $CHCl_3$ fractions were washed with water and dried over $MgSO_4$. Filtration and removal of the solvents *in vacuo* afforded crystalline *E*/*Z*-sulfone mixtures 1 (*E*/*Z*-ratio of 2) in 97% yield.

The *E*/*Z*-ratios are based on the C2-methyl-absorptions in the ^1H NMR-spectrum (Table 5).

Glc-separation (20% SE-30, 4 m, 190°C, 85 ml H_2/min) afforded pure prenyl - *E* - 2 - methyl - 1, 3 - butadienyl sulfone as a colourless crystalline unstable compound (m.p. 34.5–35.0°). IR($CHCl_3$): 1670, 1630, 1590 (C=C), 1310 and 1130 cm^{-1} (SO_2). (Found: C, 60.12; H, 7.94; S, 1589. Calcd for $C_{10}H_{16}SO_2$: C, 59.96; H, 8.05; S, 16.01; O, 15.98).

Similarly the benzyl - *E* - 2 - methyl - 1, 3 - butadienyl sulfone was obtained. ^1H NMR-data are given in Table 5.

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[a] Addition of *p*-toluenesulfonyl chloride was performed with the isoprene/SO_2–adduct. Addition of methanesulfonyl chloride to isoprene following ref. 9.

[b] ^1H NMR-data of the 3-methyl-1, 3-butadienyl sulfones will be published in a forthcoming communication.