The Different Behaviour of Cyclohexanones and their Enamines in the Reaction with Methyl (*E*)- and (*Z*)-Styryl Sulphone

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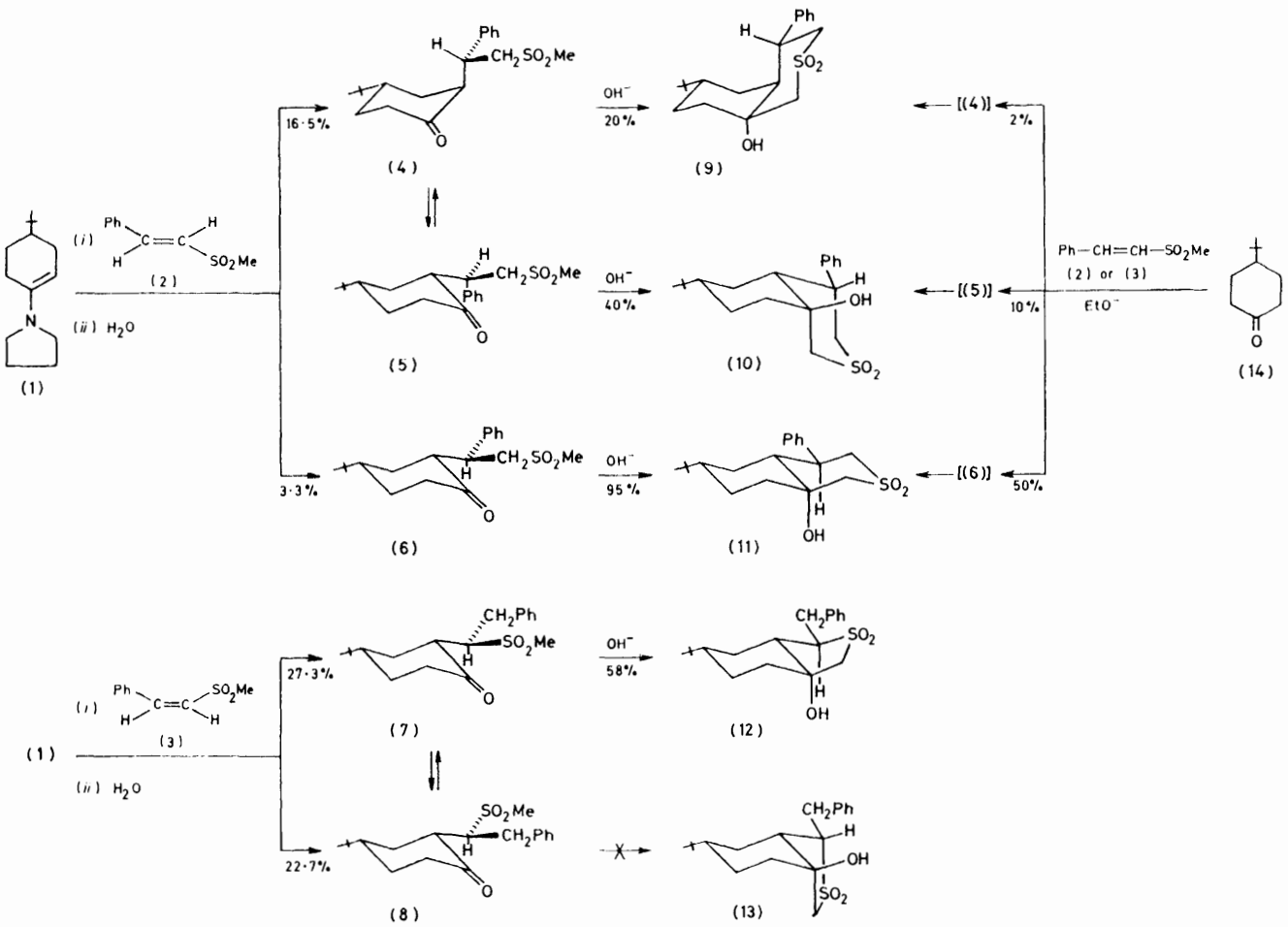
Methyl (*E*)- and (*Z*)-styryl sulphone react with 4-t-butylcyclohexanone *via* Michael addition to furnish 8a-hydroxyperhydro-2-benzothiin 2,2-dioxides. Both isomeric unsaturated sulphones add at the carbon β to the SO_2 group and give predominantly the same *trans*-fused cyclic hydroxysulphone. The results of these reactions are compared with those obtained in the synthesis of the same cyclic products *via* the enamines.

PREVIOUSLY [1] we reported that methyl (*E*)-styryl sulphone (2) attacks 4-t-butylpyrrolidin-1-ylcyclohexene (1) in both parallel and antiparallel directions, regio- and stereo-chemistry is maintained in the reaction of the sulphones (2) and (3) with the more reactive 4-t-butylcyclohexanone enolate.



SCHEME 1

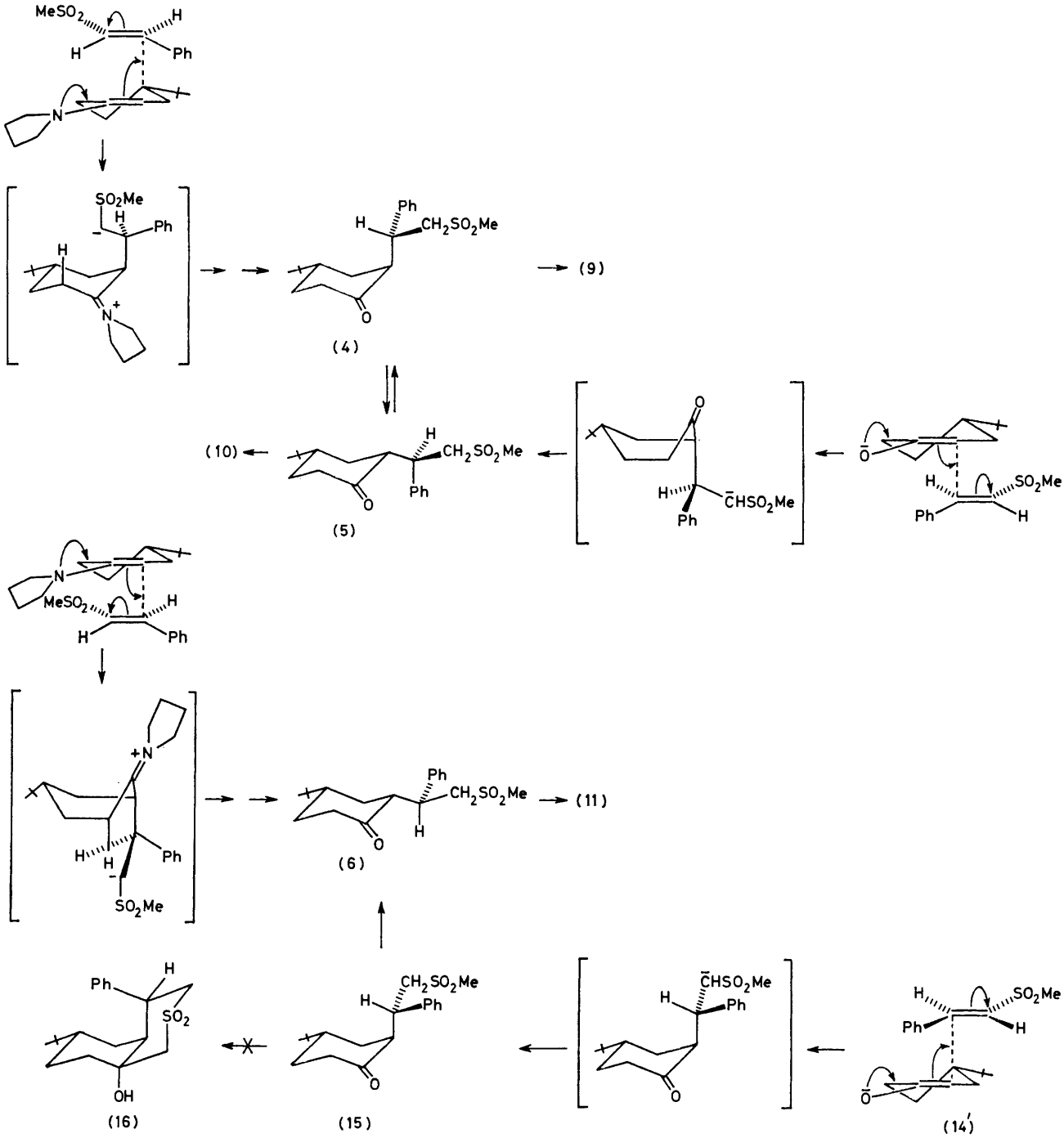
and regiospecifically at the carbon β to the SO_2 group, leading to the ketosulphones (4), (5), and (6) in yields reported in Scheme 1. The *Z*-styryl sulphone (3) also adds by both parallel and antiparallel attack, but regiospecifically at the carbon α to the SO_2 group, leading to the ketosulphones (7) and (8) [1] (Scheme 1).

On the basis of the close relationship between enamines and enolate anions,[2] we were interested to verify if this

RESULTS AND DISCUSSION

Since the ketosulphones originated from (2) or (3) and (14) underwent cyclization to hydroxysulphones in the basic reaction medium, the ketosulphones (4), (5), (6), (7), and (8) obtained from enamine (1) were also converted into hydroxysulphones, in order to compare the results of the two reactions. The configurations of the hydroxysulphones so obtained were deduced on the

basis of the following considerations. (*i*) Ketosulphone (6) furnished only one cyclic hydroxysulphone which must be the *trans*-perhydro-2-benzothiin 2,2-dioxide derivative (11), because a *cis*-cyclization would imply a strong 1,3-diaxial interaction between phenyl and hydroxy-groups.[3] (*ii*) Ketones (4) and (5), which in basic medium are in equilibrium with each other,[1] gave two cyclic products. Ketone (4) can obviously only give a *cis*-ring closure leading to the sulphone (9), whereas compound (5), in order to avoid the 1,3-diaxial interaction Ph–OH,[3] can furnish only the *cis*-isomer (10). Compounds (9) and (10) were characterized by their i.r. spectra in chloroform solutions. Only the former showed a band due to free OH, whilst a band due to OH intramolecularly bonded to SO_2 was present in the spectrum of the latter. (*iii*) Ketones (7) and (8), inverconvertible in basic medium into each other through the common α-sulphonyl carbanion,[1] furnished only one



SCHEME 2

cyclic sulphone. To avoid the 1,3-diaxial interactions $PhCH_2$–OH,[3] the ketone (7) can undergo only *trans*-ring closure to (12), whereas (8) can furnish only the *cis*-compound (13). In our opinion the product is likely to be the *trans*-compound (12), in view of easier *trans*-cyclization with respect to *cis*-cyclization when both are allowable.[3,4]

The above assignments are supported by the ^1H n.m.r. spectra of (9), (10), (11), and (12), which are nearly identical to those of the corresponding hydroxysulphones without the t-butyl group.[3]

The Michael addition of 4-t-butylcyclohexanone (14) to methyl (*E*)-styryl sulphone (2) in the presence of sodium ethoxide led to the cyclic sulphones (9), (10), and (11) in 2, 10, and 50% yield, respectively (Scheme 1). Small amounts of the ketosulphones (4), (5), and (6) were also isolated.

This remarkable stereoselectivity (11): [(9) + (10)] = 4 : 1 indicates that antiparallel and parallel attack of (2) on (14) are not equivalent, in contrast to other reactions of 4-t-butylcyclohexanone.[5] Moreover it is rather surprising that the stereoselectivity is inverted with respect to that observed in the case of the enamine reacting with the same sulphone. In our opinion these results can be understood if two different orientations in the approach of the reagents are assumed for the two routes. In the reaction of enamines with electrophilic olefins, the reagents are oriented in such a way as to minimize the separation between the opposite charges developing in the transition state, which leads to the reaction intermediate shown in Scheme 2. On the contrary, the reaction of the enolates with the same reagents implies a delocalization of the negative charge, and therefore the reagents must be oriented in such a way as to maximize the separation between the developing like fractional charges (Scheme 2). A substantially similar mechanism has already been suggested for the Michael reaction between cyclohexanone and chalcone.[6] So, for example, ketone (6) could form from (14′) not by an apparent parallel attack, but by an antiparallel attack, which, however, occurs with an orientation which satisfies the above mentioned electronic demands and avoids steric interactions between the phenyl group and the alicyclic ring. This attack would lead to (15), which cannot undergo cyclization to (16) for steric reasons, so that its fate can only be epimerization into (6) (Scheme 2). A parallel attack with the same orientation could lead to ketosulphone (5) and subsequently to the bicyclic products (9) and (10) (Scheme 2).

In the reaction mixture obtained from the enolate and the *Z*-sulphone (3), compounds (7), (8), or (12) have not been detected; only the hydroxysulphones (9), (10), and (11) were isolated (Scheme 1). Since the unreacted unsaturated sulphone was recovered as the *E*-isomer, the above results can be understood assuming that the *Z*→*E* isomerization, catalysed by the ethoxy-anion, is much faster than the reaction of the *Z*-isomer with the enolate. The catalysis by the ethoxy-anion of the *Z*→*E* isomerization, is supported by the fact that the *Z*-sulphone adds to ethanol, and the addition compound easily reacts with t-butylcyclohexanone enolate giving the hydroxysulphones (9), (10), and (11).

EXPERIMENTAL

^1H N.m.r. spectra were recorded with a Perkin-Elmer R 12B spectrometer ($SiMe_4$ internal standard; solutions in $CDCl_3$) and i.r. spectra (Nujol mulls, unless otherwise noted) with a Perkin-Elmer 257 spectrophotometer. For analytical t.l.c., plates were coated with silica gel G (Merck) and developed with benzene–acetone (90 : 10). For chromatographic columns extra-pure silica (Merck 70—230 mesh ASTM) was used as the stationary phase and benzene–acetone (90 : 10) as eluant.

Cyclization of (2R*, αS*)-cis-4-*t-Butyl*-2-(α-*phenyl*-β-*methylsulphonylethyl*)*cyclohexanone* (6).—The ketone (6) [1] (0.200 g, 0.59 mmol) was heated under reflux for 6 h with potassium hydroxide (0.400 g, 7.15 mmol) in ethanol (25 ml). The solution was concentrated *in vacuo*, diluted with water, acidified with 10% hydrochloric acid, and extracted with chloroform. Evaporation of the solvent gave 6α-*t-butyl*-8aα-*hydroxy*-4β-*phenyl*-trans-*perhydro*-2-*benzothiin* 2,2-*dioxide* (11) (0.190 g, 95%), m.p. 203 °C (from ethanol) (Found: C, 68.0; H, 8.5. $C_{19}H_{28}O_3S$ requires C, 67.8; H, 8.4%); $\nu_{max.}$ ($CHCl_3$) 3 510 cm^{-1}; $\nu_{max.}$ (Nujol) 3 510 (OH) and 1 312, 1 300, and 1 132 cm^{-1} (SO_2); δ 7.25 (5 H, m, Ar-H), 4.0 (1 H, s, OH), and 0.72 (9 H, s, CMe_3).

Cyclization of (2S*, αR*)-trans-4-*t-Butyl*-2-(α-*phenyl*-β-*methylsulphonylethyl*)*cyclohexanone* (4) *and of the* (2R*, αR*)-cis-*Stereoisomer* (5).—The ketone (4) [1] or (5) [1] (0.500 g, 1.49 mmol) was refluxed for 9 h in ethanol (50 ml) with potassium hydroxide (1 g, 17.8 mmol). After concentration under reduced pressure, dilution with water, acidification with 10% hydrochloric acid, and extraction with chloroform, the solid residue (0.450 g) was chromatographed on silica. The first fraction furnished a dehydration product of the bicyclic hydroxysulphones that, on the basis of its spectroscopic properties,[3,4] must be 6-*t-butyl*-4-*phenyl*-3,4,5,6,7,8-*hexahydro*-1H-2-*benzothiin* 2,2-*dioxide* (0.100 g, 20%), m.p. 211 °C (from ethanol) (Found: C, 71.2; H, 8.2. $C_{19}H_{26}O_2S$ requires C, 71.7; H, 8.2%), $\nu_{max.}$ 1 300, 1 280, 1 135, and 1 120 cm^{-1} (SO_2); δ 7.28 (5 H, m, Ar-H), 4.2—3.0 (5 H, complex), 2.4—1.0 (7 H, complex), and 0.75 (9 H, s, CMe_3). A subsequent fraction provided 6α-*t-butyl*-8aβ-*hydroxy*-4α-*phenyl*-cis-2-*perhydro*-2-*benzothiin* 2,2-*dioxide* (10) (0.200 g, 40%), m.p. 205 °C (from ethanol) (Found: C, 67.8; H, 8.4. $C_{19}H_{28}O_3S$ requires C, 67.8; H, 8.4%); $\nu_{max.}$ ($CHCl_3$) 3 510 cm^{-1}; $\nu_{max.}$ (Nujol) 3 552 (OH) and 1 305 and 1 145 cm^{-1} (SO_2); δ 7.25 (5 H, m, Ar-H), 4.41 (1 H, s, OH), and 0.73 (9 H, s, CMe_3). The last fraction gave 6β-*t-butyl*-8aβ-*hydroxy*-4β-*phenyl*-cis-*perhydro*-2-*benzothiin* 2,2-*dioxide* (9) (0.100 g, 20%), m.p. 227 °C (from ethanol) (Found: C, 68.0; H, 8.3%); $\nu_{max.}$ ($CHCl_3$) 3 680 and 3 510 (OH); $\nu_{max.}$ (Nujol) 3 450 (with shoulder at 3 430) (OH) and 1 315, 1 300, and 1 120 cm^{-1} (SO_2); δ 7.25 (5 H, m, Ar-H), 2.15 (1 H, s, OH), and 0.78 (9 H, s, CMe_3).

Cyclization of (2S*, αR*)-cis-4-*t-Butyl*-2-(α-*methylsulphonyl*-β-*phenylethyl*)*cyclohexanone* (7) *and of the* (2S*, αS*)-cis-*Stereoisomer* (8).—The ketone (7) [1] or (8) [1] (1.700 g, 5.05 mmol) was refluxed for 15 h with potassium hydroxide (3.40 g, 60.7 mmol) in ethanol (40 ml), and the reaction mixture was worked up as described for (4) and (5). Column chromatography of the oily residue (1.40 g) gave first a

small amount (0.200 g, 12%) of a dehydration product to which we attribute the structure of 1-*benzyl*-6-*t*-*butyl*-1,3,4,5,6,7-*hexahydrobenzo*[b]*thiophen* 2,2-*dioxide* on account of the absence of a C=C band in its i.r. spectrum,[3] m.p. 210 °C (from ethanol) (Found: C, 71.6; H, 8.1. $C_{19}H_{26}O_2S$ requires C, 71.7; H, 8.2%); $\nu_{max.}$ 1 310, 1 300, 1 288, and 1 125 cm^{-1} (SO_2). The second fraction afforded 1β-*benzyl*-6α-t-*butyl*-3aα-*hydroxy*-trans-*perhydrobenzo*[b]*thiophen* 2,2-*dioxide* (12) (1 g, 58%), m.p. 178 °C (from ethanol) (Found: C, 67.9; 8.5. $C_{19}H_{28}O_3S$ requires C, 67.8; H, 8.4%); $\gamma_{max.}$ ($CHCl_3$) 3 520 cm^{-1}; $\gamma_{max.}$ (Nujol) 3 500 (OH) and 1 300, 1 140, 1 130, and 1 120 cm^{-1} (SO_2); δ 7.38 (5 H, m, Ar-H), 4.25—3.9 (1 H, dd, *H*C–CH_2–Ph), 5.95 (1 H, s, OH), and 0.9 (9 H, s, CMe_3).

Michael Reaction of Methyl (E)-(2) *and* (Z)-*Styryl Sulphone* (3) *with* 4-*t*-*Butylcyclohexanone* (14).—The ketone (14) (4.62 g, 30 mmol) was dissolved in a solution of sodium ethoxide in ethanol [from Na (0.575 g, 25 mmol) and EtOH (40 ml)]. After 30 min at room temperature (*E*)- (2) [7] or (*Z*)-sulphone [8] (3) (3.64 g, 20 mmol) was added and the mixture was heated for 30 min on an oil-bath (external temperature 100 °C). After acidification with 10% hydrochloric acid, concentration *in vacuo*, and extraction with chloroform, an oily mixture (8.26 g) was obtained. A portion (1 g) of this mixture was repeatedly chromatographed on silica. Besides unchanged 4-t-butylcyclohexanone and a small amount of methyl (*E*)-styryl sulphone, the hydroxysulphones (9), (10), and (11), and the dehydration product (m.p. 211 °C) with the ketosulphones (4), (5), and (6) were isolated in the yields reported in the Table.

Percentages of reaction products from the Michael reaction

Starting unsaturated sulphone	Ketones (4), (5), and (6), and dehydration product	Bicyclic hydroxy-sulphones		
		(11)	(10)	(9)
Z	10.24	45.91	12.06	1.89
E	10.84	49.49	9.68	1.51

The yields of dehydration product increased greatly when the reaction time was prolonged for more than 30 min; with a shorter reaction time a greater amount of the ketosulphones was obtained.

Reaction of Methyl (Z)-*Styryl Sulphone* (3) *with Sodium Ethoxide*.—The (*Z*)-sulphone (1.82 g, 10 mmol) was dissolved in a solution of sodium ethoxide in ethanol [from Na (0.287 g, 12.5 mmol) and dry EtOH (40 ml)]. The solution was heated for 30 min on an oil-bath (external temperature 100 °C), acidified with 10% hydrochloric acid, concentrated under reduced pressure, and extracted with chloroform. The residue obtained after elimination of the solvent (2.20 g) showed two spots on t.l.c. The two compounds were separated by column chromatography; the major component was identified as an addition product of ethanol to the αβ-unsaturated sulphone (1.70 g, 75%), m.p. 48 °C (Found: C, 57.7; H, 7.1. $C_{11}H_{16}O_3S$ requires C, 57.9; H, 7.1%); $\nu_{max.}$ 1 290 and 1 118 cm^{-1} (SO_2); δ 7.30 (5 H, m, Ar-H), 5.05—4.75 (1 H, dd, *H*C–SO_2Me), 3.75—3.0 (7 H, complex, $PhCH_2$, CH_2Me, and SO_2CH_3), and 1.17 (3 H, t, CH_2Me_3).

On the basis of its n.m.r. spectrum, which is analogous to those of similar products,[9] this addition compound is assigned the structure *methyl* (α-*ethoxy*-β-*phenylethyl*) *sulphone*. The minor component (0.450 g, 25%) was identified as methyl (*E*)-styryl sulphone.

Reaction of Methyl (α-*Ethoxy*-β-*phenylethyl*) *Sulphone with* 4-*t*-*Butylcyclohexanone* (14).—The ketone (14) (4.62 g, 30 mmol) was dissolved in a solution of sodium ethoxide in ethanol [from Na (0.575 g, 25 mmol) and dry EtOH (40 ml)]. After 30 min at room temperature, methyl (α-ethoxy-β-phenylethyl) sulphone (4.56 g, 20 mmol) was added and the mixture was heated for 30 min on an oil-bath (external temperature 100 °C). The reaction mixture was worked up as described for the Michael reactions, and furnished in nearly identical yields the same products obtained from the αβ-unsaturated sulphones (2) or (3).

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