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NUCLEOPHILIC ADDITION TO STYRYL SULPHONES. PART I. A STUDY ON THE REGIOCHEMISTRY.

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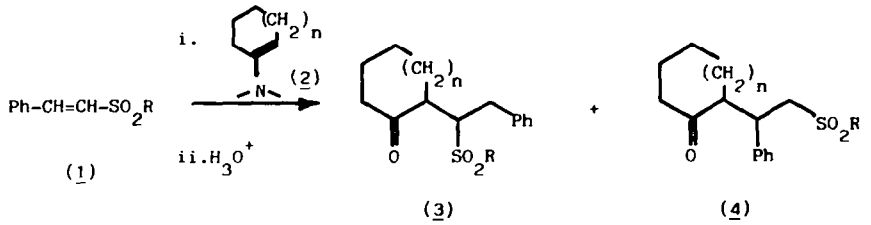
Abstract - Styryl sulphones undergo nucleophilic addition, with the nucleophile adding at the α- or the β-position, with respect to the sulphone group; β-attack is normally favoured over α-attack. Factors which can change the regioselectivity in favour of the addition of the nucleophile to the α-position are discussed for heteronucleophiles as well as carbon nucleophiles.

INTRODUCTION

We have shown in a previous paper[1] that styrylsulphones (1) undergo nucleophilic attack by enamines of cyclic ketones (2) at both the α- and β-positions, with respect to the sulphone group, to give, after hydrolysis, the adducts (3) and (4) respectively (Scheme 1).

Other reactions between styryl sulphones and nucleophiles are reported in which β- and α-adducts are formed simultaneously with poor selectivity,[2,3] or in which either β- or α-adducts are selectively obtained, depending upon the conditions[4-8]. In addition, there are cases in which the structure of the product has not been unambiguously demonstrated, but it has been deduced on the assumption that β-attack only was taking place.[4,9,10]

It is clear from this picture that not only enamines, but any nucleophile in general can add across the double bond of a styrylsulphone to give α- and/



a ; R = CH_3

b ; R = Ph

n = 0,1

Scheme 1

or β-adducts: in this paper we try to point out the factors which determine the regiochemical course of the reaction.

RESULTS AND DISCUSSION

If we admit that any nucleophile $\bar{Z}$ can react with a styryl sulphone as in scheme 2, in which the slow step is addition of the nucleophile to give the intermediate carbanions (5) and (6), then the ratio β-adduct/α-adduct is equal to k_β/k_α; this ratio can be approximated to the ratio K_β/K_α, where K_β is the ionization constant of the reference carbon acid RSO_2CH_3 ($K_\beta = 10^{-29}$ when R = Ph)[11] and K_α is the ionization constant of toluene ($K_\alpha \cong 10^{-44}$).[12] According to this approach, which has already been applied to the addition of nucleophiles to several disubstituted ethenes X-CH=CH-Y,[13] the ratio β-adduct/α-adduct should be equal to 10^{15}; only formation of the β-adduct is therefore expected to be observed.

It is important to recognize that this approach is based on several assumptions:

i - protonation of the carbanions (5) and (6) is fast.

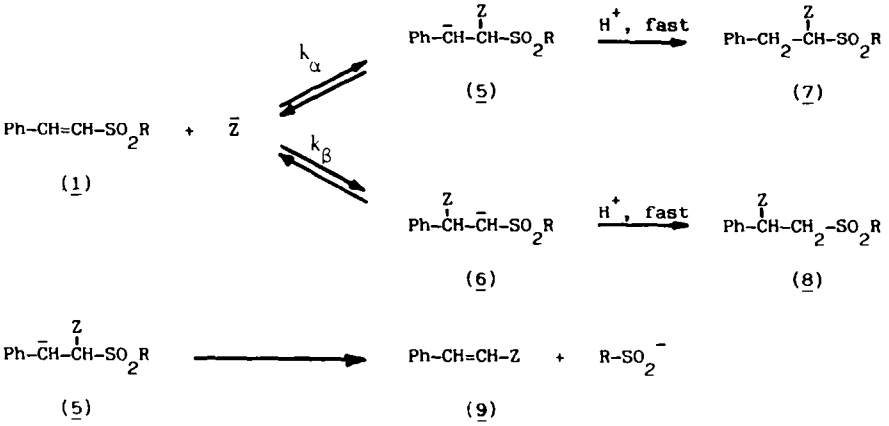
ii - the adducts (7) and (8) are not in equilibrium.

iii - the structure of the two transition states for the slow addition step resembles that of the intermediates (5) and (6).

iv - steric and electronic effects of the Z grouping on the stability of the carbanions (5) and (6) are negligible.

When one, or more, of these conditions is not fulfilled, the prediction that only β-adduct is to be formed is no longer true.

Thus it is clear why, for example,



a : R = CH_3

b : R = Ph

c : Z = OMe ; R = Ph

d : Z = OEt ; R = Ph

e : Z = SPh ; R = Ph

Scheme 2

Stirling and his coworkers obtained only β-adducts (8c,d,e) by the base catalyzed addition of alcohols and thiols to phenylstyryl sulphone (1b) in protic medium,[6] while, with methoxide and thiophenoxide in dimethyl sulfoxide, Julia and coworkers obtained an addition - elimination product (9c,e) which can only result from α-attack[7] (scheme 2). In the protic solvent the carbanion (6c,d,e) is rapidly protonated to give the normal product (8c,d,e); in absence of a proton donor, an equilibrium is established between the two intermediates (5c,e) and (6c,e), which leaks through the elimination of benzene sulphinate from the benzylic carbanion (5c,e): so the alkene (9c,e) is the only product even if (5c,e) is only present at the equilibrium in exceedingly small amount.

In order to prove this sequence we have treated (β-methoxy-β-phenylethyl)-phenyl sulphone (8c) with sodium in dimethylsulphoxide. Deprotonation at the carbon α to the sulphone group gives (6c) which is in equilibrium with (5c); eventually elimination of benzene sulphinate again gives β-methoxystyrene (9c). Further reaction of the enolether leads to a complex mixture of identical composition to that obtained by addition of sodium methoxide to phenylstyryl sulphone (1b) in DMSO.

In the reaction of styryl sulphones with enamines, formation of α-adducts can not be explained on the same ground for it is known that dipolar intermediates, in the addition of enamines to electrophilic olefins, are protonated by fast intramolecular proton transfer from a carbon atom adjacent to the immonium group[14] (scheme 3).

It is possible that, in this case, the "anomalous" formation of α-adducts is due to an electrostatic interaction between the positively charged nitrogen atom and one of the electron rich oxygens of the sulphonyl group, which stabilizes the intermediate (10) and the

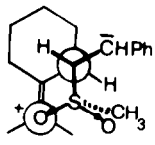


Fig.1

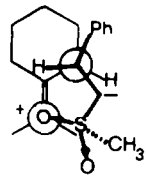
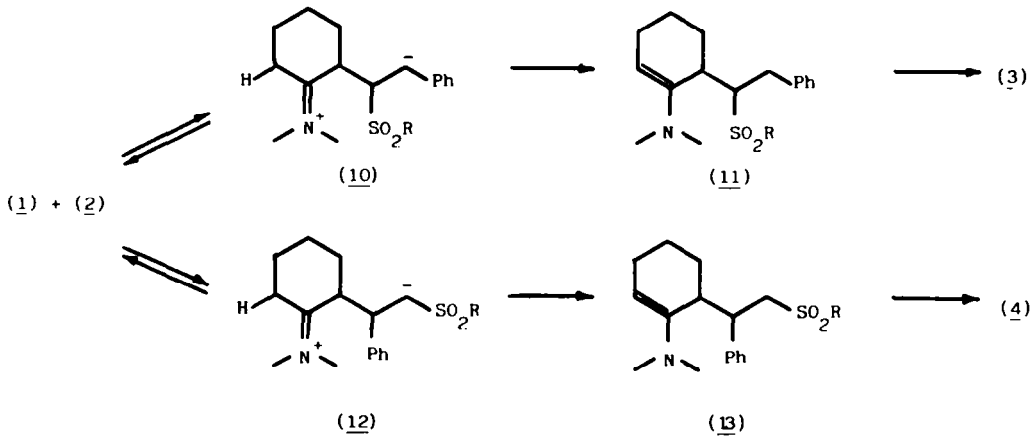


Fig.2

transition state leading to it (fig.1). Such interaction, in the zwitterion (12) originated by a β-attack, would involve the formation of a less favoured seven-



Scheme 3

Table

Addition of pyrrolidin-1-yl-cyclohexene to (E)- and (Z)-PhCH=CHSO$_2$R.

solvent	R	configuration of the alkene	ß-adduct (%)	α-adduct (%)
none	CH_3	E	< 20	> 80
none	CH_3	Z	< 20	> 80
none	Ph	E	< 20	> 80
none	Ph	Z	< 20	> 80
dioxane*	CH_3	E	22	78
dioxane*	CH_3	Z	44	56
dioxane*	Ph	E	86	14
dioxane*	Ph	Z	71	29
ethanol	CH_3	E	> 95	< 5
ethanol	CH_3	Z	> 95	< 5
ethanol	Ph	E	> 95	< 5
ethanol	Ph	Z	> 95	< 5

* see reference 1.

membered ring (fig.2).

The dependence of the product distribution upon the medium, in the reaction of pyrrolidin-1-yl-cyclohexene (2, n=1) with E and Z styryl sulphones (see scheme 1), seems to be consistent with our hypothesis (Table). In absence of solvent, when the electrostatic interaction must be strong because the reacting species are not shielded by surrounding solvent molecules, at least 80% of the product consists of α-adduct; in dioxane the percentage of α-adduct varies from 14% to 78%; finally in ethanol where the zwitterions are strongly solvated, the interaction is greatly reduced and the fraction of α-adduct does not exceed 5%.

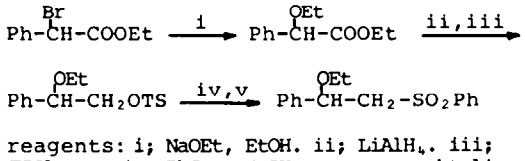
Further support to this hypothesis is given by the reaction between methyl styryl sulphone (1a) and cyclohexanone enolates (scheme 4). The nucleophile is structurally similar to an enamine, but the electrostatic interaction is no longer possible since the heteroatom is not positively charged in the transition state; thus exclusively the β-adduct (4a) is formed. In the basic medium (4a) reacts further to give the bicyclic sulphones (14), (15) and (16).[15]

EXPERIMENTAL

Melting points are uncorrected. Unless otherwise stated, I.R. spectra were registered on a Perkin Elmer 297 double beam spectrophotometer and ^{1}H N.M.R. spectra were recorded at 60 MHz in $CDCl_3$, with TMS as internal standard on a JEOL-JNM-C-60 HL spectrometer. Silica gel G (Merck-Stahl) was used for T.L.C. with benzene and acetone (9:1) as eluent; column chromatographies were performed on Silica gel (Merck, 70-325 mesh ASTM) with the same eluent.

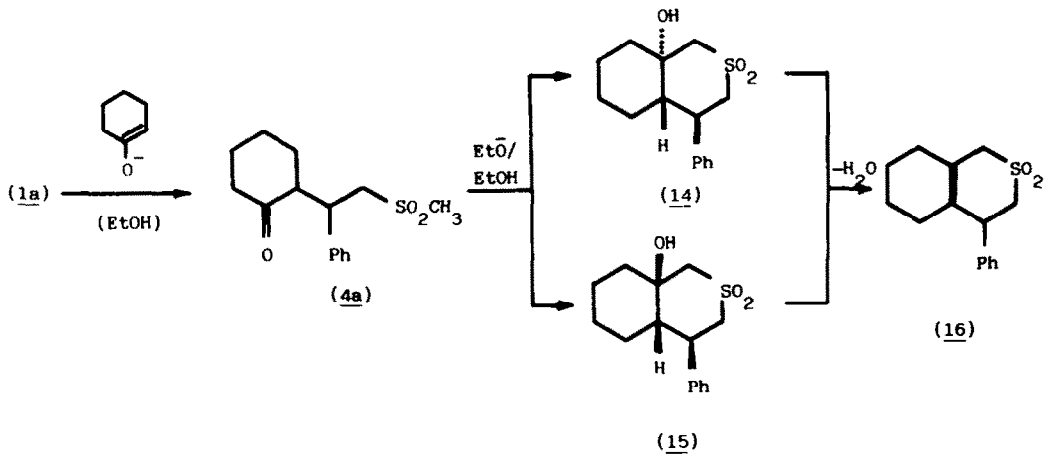
Starting materials. Phenyl (E)- and (Z)-β-styryl sulphones[16] and methyl(Z)-β-styryl sulphone[17] were synthesized as described in the literature. Methyl (E)-β-styryl sulphone, m.p. 79-80° (lit.[18] 79-80°) was obtained from α-methyl-sulphonyl acetophenone[19] by reduction, with $NaBH_4$, to the hydroxy-sulphone[18], followed by chlorination with $SOCl_2$ and dehydrochlorination with triethylamine.

Synthesis of authentic phenyl (2-phenyl-2-ethoxy ethyl) sulphone (8d). The compound has been synthesized in 5 steps from ethyl α-bromophenylacetate (scheme 5)



reagents: i; NaOEt, EtOH. ii; $LiAlH_4$. iii; TSCl, py. iv; PhSNa, EtOH. v; monoperphtalic acid.

Scheme 5



Scheme 4

Ethyl α-bromophenylacetate (2.43 g, 0.01 mol) and an equimolar amount of sodium ethoxide were refluxed in dry ethanol for 1 hr; when reaction was complete the solution was concentrated under reduced pressure and diluted with ice-cold water; extraction with chloroform gave crude α-ethoxy ester, pure by T.L.C. This compound, without further purification, was reduced with $LiAlH_4$ to the corresponding alcohol which, by treatment with tosyl chloride in pyridine, was eventually converted to 2-phenyl-2-ethoxyethyl-p-toluene sulphonate in 75% yield (oil). I.R. ν_{MAX} (cm^{-1}): 1180, 1190 and 1360 ($-SO_2-$ stretching). N.M.R.(δ): 1.10 (t,3H); 2.40 (s, 3H); 3.40 (q, 2H); 4.10 (d, 2H); 4.30-4.60 (dd, 1H); 7.10-7.90 (m, 9H). The tosylate (3.20 g, 0.01 mol) was refluxed for 2 hr with a solution of sodiumthiophenoxide (1.1 equivalent) in ethanol (50 ml); dilution with water and extraction with chloroform gave, in 80% yield, phenyl (β-ethoxy-β-phenylethyl)sulphide, which was purified by column chromatography (eluent: benzene). N.M.R. (δ): 1.10 (t, 3H); 3.10-3.50 (m, 4H); 4.25-4.50 (dd, 1H); 7.00-7.40 (m, 10H). The sulphide (2.60 g, 0.01 mol) in ether (20 ml) was oxidized with monoperphtalic acid[20] in ether to give the product in 90% yield; m.p. 100°(from ethanol) lit.[6] 100°C. (Found C, 66.2; H, 6.25. $C_{16}H_{18}O_3S$ requires C, 66.1; H, 6.30); I.R. ν_{MAX} (cm^{-1}): 1140, 1293 ($-SO_2-$ stretching). N.M.R. (δ): 0.9 (t, 3H); 3.0-3.9 (m, 4H); 4.7-5.0 (dd, 1H); 7.2-8.0 (m, 10H).

Addition of alcohols to phenyl styryl sulphone in alcohol.
(E)- or (Z)-phenyl styryl sulphone (2.44 g, 0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (30 ml) are refluxed for 30'; the solution was cooled, acidified with 10% HCl, concentrated under reduced pressure and extracted with chloroform. Evaporation of the extracts and separation by column chromatography gave phenyl (β-ethoxy-β-phenyl ethyl) sulphone (8d) (75%), identical with an authentic specimen, the remaining material being E-phenyl-β-styryl sulphone≠. When MeONa in methanol was used in place of NaOEt/EtOH, the corresponding methoxy adduct (8c) was obtained in 80% yield, together with E-alkene≠. The β- structure was assigned to this adduct on the basis of its N.M.R. spectrum which was analogous to that of the ethoxy adduct (8d). (8c) had m.p. 80-82° (from methanol) lit.[6] 76°C. (Found: C, 65.1; H, 5.90. $C_{15}H_{16}O_3S$ requires C, 65.2; H, 5.84). I.R. ν_{MAX} (cm^{-1}): 1135, 1300 ($-SO_2-$stretching). N.M.R. (δ): 3.05 (s, 3H); 3.3-3.5 (2d, 2H); 4.5-4.75 (dd, 1H); 7.0-7.9 (m, 10H). By refluxing phenyl-β-styryl sulphone, (E) or (Z), in the appropriate alcohol, without base added, after 24 hr the same adducts are obtained, albeit in low yields (10-20%).

Base catalyzed addition of thiophenol to phenyl styryl sulphone.
Triethylamine (0.1 ml, 0.72 mmol) was added to (E)- or (Z)-phenyl β-styryl sulphone (0.39 g, 1.6 mmol) and thiophenol (0.19 ml, 1.8 mmol) in dry benzene and the solution was kept at room temperature for 20 hr. Evaporation of the solvent gave a residue consisting of 3 products which were separated by column chromatography: the first prod-

≠ Isolation of unreacted alkene possessing E configuration also in the reaction with the Z-isomer is consistent with the reversibility of the addition of the nucleophile (see scheme 2).

uct (40%) was phenyl(β-phenyl sulphenyl) -β-phenyl ethyl)sulphone (8e), m.p. 137°C (from ethanol) lit.[6] 140°C. (Found: C, 67.7; H, 5.20; $C_{20}H_{18}S_2O_4$ requires C, 67.8, H, 5.12) I.R. ν_{MAX} (cm^{-1}): 1140, 1300 ($-SO_2$-stretching) N.M.R. (δ): 3.65-3.90 (2d, 2H) 4.5-4.8 (dd, 1H) 6.9-7.9 (m, 15H).
The second product was (E)-phenyl β-styryl sulphone (40%); the third one was not identified, but the possibility of it being the α-adduct is excluded on the basis of I.R. and N.M.R. analysis. In absence of triethylamine no addition was observed and unreacted styryl sulphone is recovered together with diphenyl disulphide. In order to confirm its structure the adduct (8e) was oxidized to the corresponding bis-sulphone $Ph-CH(SO_2Ph)-CH_2-SO_2Ph$[6]. This compound exhibited physical and spectroscopic properties different from those of the isomer $Ph-CH_2-CH(SO_2Ph)_2$, synthesized as follows: 2,2-bis(phenyl sulphonyl)styrene[21] (0.77 g, 2 mmol) and TEAF[22] ($HCOOH-NEt_3$ azeotrope, 0.52 g, 3 eq) in DMF (4 ml) were refluxed for 2.5 hr. Volatile materials were removed under reduced pressure while the residue was dissolved in benzene (10 ml); this solution was washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave quantitatively the product[23], m.p. 140-142° (from methanol). (Found: C, 62.2; H, 4.70; $C_{20}H_{18}O_4S_2$ requires: C, 62.2; H, 4.70). N.M.R. (δ): 3.35 (d, 2H), 4.53 (t, 1H), 7.13 (m, 15H). Reduction of 2,2-bis(phenyl sulphonyl)styrene with TEAF is reported[22] to give 1-phenyl sulphonyl-1-phenyl sulphenyl-2-phenyl ethane; however we have never observed formation of this compound.

Addition of ethoxide, methoxide and thiophenoxide to (E)- and (Z)-phenyl-styryl sulphones in DMSO.
Reactions were carried out as described in the literature [7]; T.L.C. of the crude reaction (eluent: cyclohexane/dichloro methane/ethyl acetate 15:15:1) showed a complex mixture of products: starting materials and β-adducts were not present. No attempts have been made to isolate the products. No reaction is observed in other aprotic solvents such as ether, dioxan, benzene and THF.

Reaction of 1-phenyl sulphonyl-2-methoxy -2-phenyl ethane with sodium in DMSO.
Sulphone (2.76 g, 0.01 mol) in DMSO (10 ml) was added to a suspension of sodium (0.23 g, 0.01 mol) in DMSO (20 ml). The reaction mixture was stirred at room temperature for 48 hr, poured into ice water and extracted with dichloromethane. Evaporation of the solvent under reduced pressure gave an oil which, on T.L.C. showed the same composition as the mixture obtained from the reaction of phenyl-β-styryl sulphone and sodium methoxide in DMSO.

Reaction of (E)- and (Z)-methyl-β-styryl sulphone (1a) and (E)- and (Z)-phenyl-β-styryl sulphone (1b) with pyrrolidin-1-yl-cyclohexene.
A. Without solvent. Neat sulphone (0.01 mol) and enamine (0.01 mol) were heated at 80° for 24 hr. The crude reaction mixture was hydrolyzed at room temperature with 10% HCl and extracted with chloroform: evaporation of the extracts gave a residue which was purified by column chromatography. Ketones (4a) or (4b) and (3a) or (3b) were obtained (see table) (Yield 50÷60%).
B. In ethanol. Sulphone (0.01 mol) and enamine (0.01 mol) in dry ethanol were refluxed for 3 hr; the mixture was concentrated under reduced pressure. The residue was hydrolyzed with 10% HCl and extracted with chloroform: removal of the solvent and column chromatography gave the products (table) (yield 80÷90%).

Reaction of (E)- and (Z)-methyl styryl sulphone (1a) with cyclohexanoneenolate.
Cyclohexanone (2.94 g, 0.030 mol) was dissolved in 0.625 M sodium ethoxide (40 ml, 0.025 mol); after 30' (E)- or (Z)-alkene was added (3.64 g 0.020 mol) and the solution was refluxed for 30'. The usual work-up gave a residue (5.50 g) which was purified by column chromatography: three products were isolated together with minor amounts of unreacted starting materials: 8a-α-hydroxy-4-β-phenyl-trans-2-thiadecalin 2,2 dioxide (14), (65%), m.p. 172-3° (from ethanol)[15]; 8a-β-hydroxy-4-β-phenyl-cis-2-thiadecalin 2,2 dioxide (15), (20%), m.p. 174-6° (from ethanol)[15]; 4-phenyl-Δ4a(8a)-2-thiaoctalin 2,2 dioxide (16), (10%), m.p. 178-9° (from ethanol)[15].

Evidences for a kinetic control in the addition of pyrrolidin-1-yl-cyclohexene to styryl sulphones.
β-adduct from the enamine and (E)-methyl styryl sulphone can be isolated, prior to hydrolysis, by carrying out the reaction in dioxane for 24 hr, and adding ether to precipitate the solid product (I.R. ν_{MAX}, (cm^{-1}): 1650 (C=C stretching); 1305, 1290, 1130 and 1125 ($-SO_2$- stretching); absence of C=O absorption. Hydrolysis of this product gave the ketone (4a)). This enaminic β-adduct is recovered unchanged after 24 hr, at reflux in dioxane. Enaminic α-adducts on the contrary, have never been isolated as such. The reaction between pyrrolidin-1-yl cyclohexene and (E)-methyl styryl sulphone, in dioxane, has been followed by aliquoting the reaction mixture after 3 hr, 24 hr and 72 hr; the aliquots were hydrolyzed and analyzed by H.P.L.C. (silica A column 0.26x25 cm; n-hexane and ethanol 95:5; flow 1 ml/min. (E)-methyl styryl sulphone had retention time 5.6'; α-adducts had retention time 5.3' and β-adducts 9.3'). The chromatographic analysis shows that the ratio β-adducts/α-adducts is constant during the reaction.

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