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NUCLEOPHILIC ADDITION TO STYRYL SULPHONES. PART II. REGIO- AND STEREOCHEMISTRY OF THE ADDITION OF ENAMINES FROM 4-SUBSTITUTED CYCLOHEXANONES.

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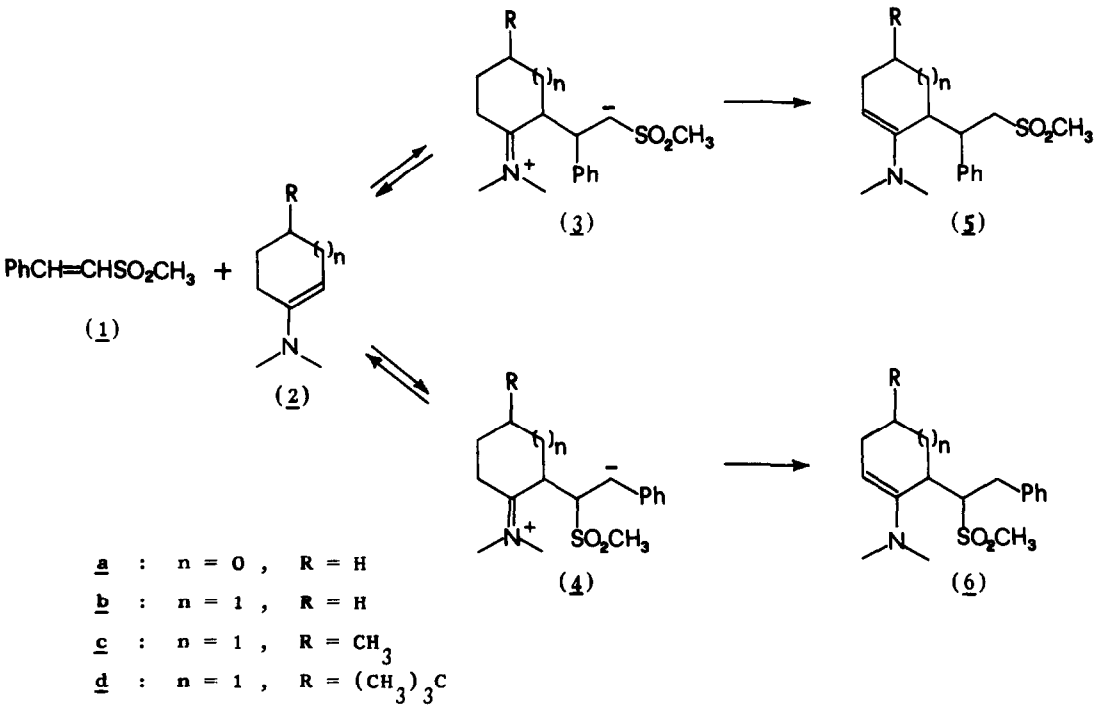
Abstract - Formation of β- and α-adducts in the reactions of styryl sulphones with enamines from 4-alkylcyclohexanones is reexamined. Steric effects, electrostatic interactions between the nitrogen atom of the enamine and the oxygen atoms of the sulphone group, and medium effects contribute to the regioselectivity of the reaction.

INTRODUCTION

It has been shown[1] that E- and Z-methyl-β-styryl sulphone (1) react with enamines from cyclohexanone (2b) and



a : n = 0 , R = H
b : n = 1 , R = H
c : n = 1 , R = CH_3
d : n = 1 , R = $(CH_3)_3C$

Scheme 1

cyclopentanone (2a) at both the β- and α- carbons, with respect to the sulphone group, to give the adducts (5a,b) and (6a,b) respectively (scheme 1).

We have pointed out[2] that, in nucleophilic addition to styryl sulphones, formation of β-adducts should be overwhelmingly favoured over that of α-adducts, due to the high carbanionic character of the transition state of the slow addition step, which closely resemble the intermediates. We have proposed[2] that in the reaction with enamines, the unexpected formation of α-adducts in considerable yields, particularly in aprotic solvents or in absence of solvent, may be due to an electrostatic interaction between the positively charged nitrogen atom and the electron rich oxygens[3] of the sulphone group which stabilizes the intermediate, and hence the transition state (fig.1). A similar interaction in the addition at the β-position would require the formation of a less favoured seven membered cyclic transition state (fig.2).

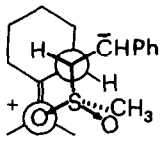


fig. 1

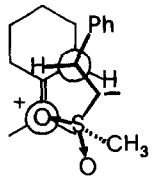


fig. 2

Our interpretation however, is apparently not supported by the result of the reaction with enamines from 4-t-butylcyclohexanone[4]. Here, surprisingly, the position at which nucleophilic attack occurs depends upon the configuration of the alkene: with the E-isomer only β-adducts (5d) are obtained (three diastereoisomers) while with the Z-alkene three diastereoisomeric α-adducts (6d) are the main products.

This result prompted us to investigate in more detail the addition of enamines to β-styryl sulphones; we are now able to account for the unusual dependence of the regiochemistry of addition upon the configuration of the electrophile.

RESULTS

Our results are collected in table 1 and 2.

Table 1 shows that in acetonitrile, the direction of attack in the reaction with E-sulphone, and, to a less extent,

Table 1. Reactivity of enamines from 4-substituted cyclohexanones in CH_3CN.

entry	substituent	configuration of the alkene	absolute yield (%)			relative yield (%)		reaction time (hr)
			β*	α*	β*+α*	β*	α*	
1	hydrogen	E	8.68	31.32	40	21.7	78.3	24
	(2b)	Z	19.0	22.0	41	46.3	53.7	24
2	methyl	E	0.72	5.28	6	12	88	24
	(2c)	Z	2.38	30.62	33	7.2	92.8	24
3	t-butyl	E	19.8	0	19.8	100	0	24
	(2d)	Z	3.0	47.0	50	6	94	24

* mixture of diastereoisomers.

Table 2. Reactivity of the enamine from 4-t-butylcyclohexanone in different media.

entry	solvent	configuration of the alkene	absolute yield (%)			relative yield (%)		reaction time (hr)
			β*	α*	β*+α*	β*	α*	
1	CH_3CN	E	19.8	0	19.8	100	0	24
		Z	3.0	47.0	50	6	94	24
2	EtOH	E	30	0	30	100	0	6
		Z	90	5	95	94.7	5.3	3
3	none	E	10	40	50	20	80	24
		Z	5	45	50	10	90	24

* mixture of diastereoisomers.

with the Z-sulphone, is specifically determined by the size of the substituent on the 4-position of the cyclohexene ring. So, with the former isomer, formation of α-adducts is preferred with the unsubstituted enamine (entry 1) or with the 4-methyl compound (entry 2) but β-adducts are formed when the substituent is the bulky t-butyl group (entry 3). With the Z-alkene, on the contrary, both enamines (2c) and (2d) show a similar preference for reaction at the α-position, while selectivity is lost with the unsubstituted compound (2b).

Table 2 shows that, in the reaction of pyrrolidin-1-yl-4-t-butyl cyclohexene with both E- and Z-sulphones, the regiochemistry is solvent dependent. Thus, whereas in acetonitrile the two isomers give different products, in ethanol they both react almost exclusively at the β-position and in absence of solvent reaction at the α-position is preferred.

Absolute yields and reaction times, in both table 1 and table 2 show that the Z-sulphone is generally more reactive than the E-isomer and that reactions are faster in ethanol than in acetonitrile or without solvent.

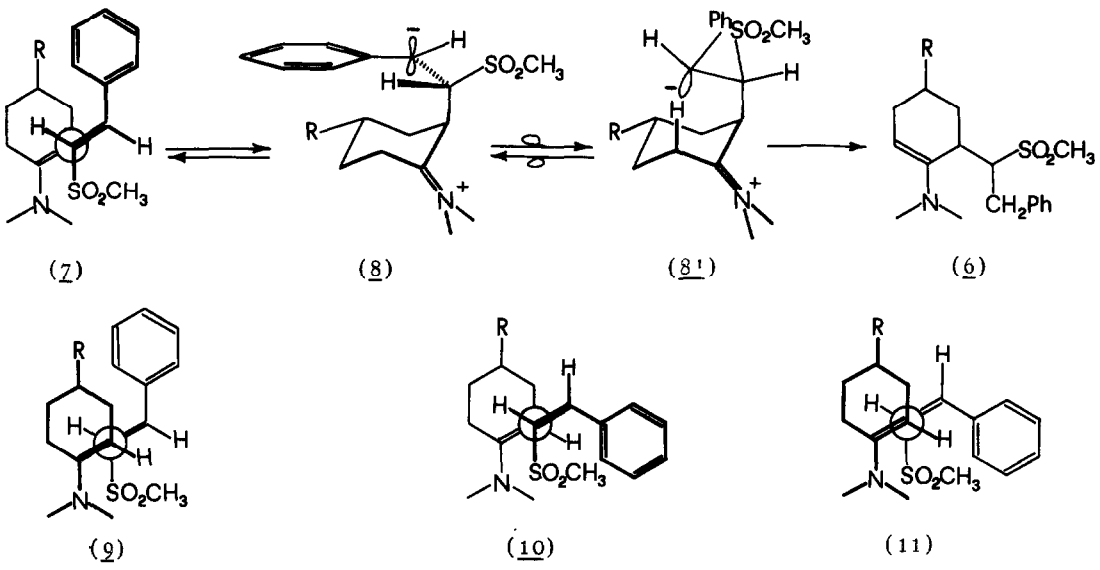
DISCUSSION

These results can be understood with a careful examination of the stereochemical requirements for the attack of the enamine on the electrophilic olefin and for the following intra- or intermolecular protonation of the zwitterions.[5,6]

Let us examine first the formation of α-adducts.

The electrostatic interaction between the sulphone group and the positively charged nitrogen atom, which assists the formation of α-adducts, requires that the sulphone group should be oriented towards the nitrogen atom of the enamine (scheme 2).

Thus, with the E-alkene, in the case of an axial attack the reagents will approach as in (7), giving the zwitterion (8). In order to provide maximum stabilization of the incipient carbanion it is also necessary for the benzene ring to be orthogonal with the occupied p orbital centered on the adjacent sp^2 carbon. Inspection of molecular models shows that this is



Scheme 2

possible in (7) and (8) only when the R group is hydrogen or methyl; the bulky tertiary butyl group prevents the correct alignement of the aromatic ring and stabilization of the carbanion is reduced. Similar conclusions can be drawn for the equatorial attack (see (9)), although this would lead to an intermediate with boat conformation.

Therefore, in the reactions with the E-alkene, formation of α-adducts is facile for the enamines from cyclohexanone (2b) and 4-methylcyclohexanone (2c) (see table 1), but it is inhibited for the 4-t-butyl derivative (2d).

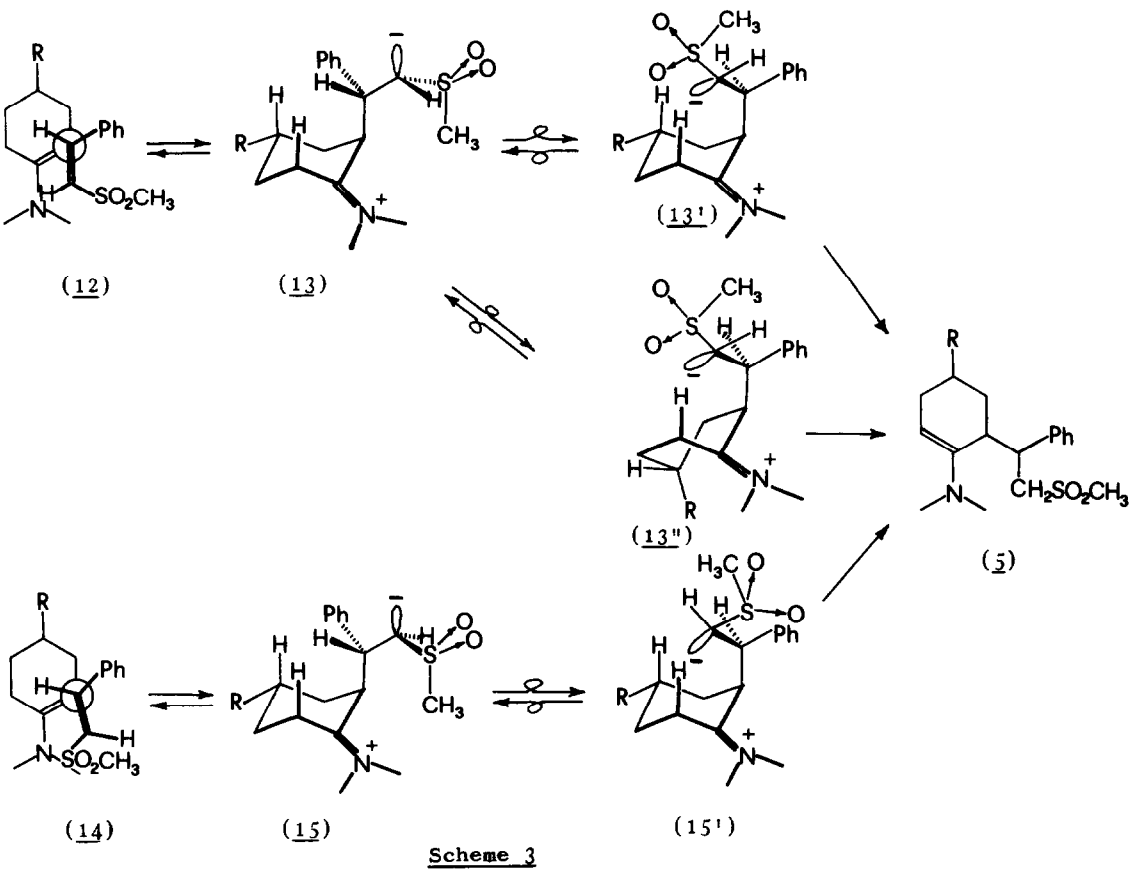
This analysis seems to be contradicted by the reaction of the 4-t-butyl compound in absence of solvent (table 2 entry 3). It is conceivable, however, that with the reagents not shielded by solvent molecules, the electrostatic interaction could be so strong as to make up energetically for the reduced stabilization of the incipient carbanion.

The situation is different in the reaction with the Z-alkene (scheme 2). Here being the benzene ring oriented away from the R group in both axial (10) and equatorial (11) approach, the optimum alignement is always possible, whatever the size of R. Thus formation of α-adducts is always preferred (table 1; table 2, entries 1 and 3), an exception being the reaction in ethanol (table 2, entry 2) which will be discussed later.†

Let us consider now the formation of β-adducts (scheme 3); we will examine first the reactions with Z-sulphone.

Axial attack (12) leads to the zwitterion (13). In this intermediate the lone pair of the β-sulphonyl carbanion occupies an sp^3 orbital bisecting the O-S-O angle[7]. In absence of a proton donor the product (5) can be formed by intramolecular proton transfer only if the intermediate adopts the conformation (13'),with a severe ste

† According to this interpretation, α-adducts formed from pyrrolidin-1-yl-4-t-butyl cyclohexene and (Z)-methyl-β-styryl sulphone possess configurations different from those originally assigned.[4] The correct configurations for the products indicated in ref.[4] with the numbers (4), (5) and (6) are: (2R*, αS*), (2S*, αS*) and (2S*, αR*) respectively. These compounds, unfortunately, are not suitable for X-ray analysis, which would confirm the proposed structures.



Scheme 3

ric interaction between the sulphone group and the axialhydrogen on the position 4 in the cyclohexane ring. Alternatively, when R=H, the proton shift can take place through the boat conformation (13"). In an equatorial attack an intermediate possessing a boat conformation is in any case obtained. As a result β-addition can hardly compete with α-addition (table 1; table 2, entries 1 and 3).

In the reactions with the E-sulphone formation of β-adducts is again disfavoured (table 1) except with the enamine from 4-t-butylcyclohexanone. In this case however the proton shift could take place in the conformer (15') where there are no interactions between the sulphone group and the ring; therefore it is likely that preference for α-addition is due to the steric interaction between the sulphone group and the heterocyclic ring which hinders the axial approach (14) leading to (15). Equatorial attack is also difficult since it would give a zwitterion with a boat conformation.

With the enamine from 4-t-butylcyclohexanone the zwitterion (8) resulting from α-addition is so destabilized by the interaction between phenyl and t-butyl group that only attack at the β -position is possible although with low yields.

Finally in protic medium β-attack is preferred with both E- and Z-sulphones (table 2, entry 2). This is the consequence of two factors: the electrostatic interaction[2] which favours α-addition is reduced because zwitterions are strongly solvated in this medium, and protonation by the solvent can replace the intramolecular proton shift. In this medium the product distribution reflects the greater intrinsic stability of the α-sulphonyl carbanion (3d) as compared to the benzylic one (4d) (scheme 1).

CONCLUSIONS

In the reactions of enamines with styryl sulphones, formation of α-adducts is preferred whenever an electrostatic interaction between the positively charged nitrogen atom and the oxygen of the sulphone is possible. When this interaction cannot assist the α-addition, β-adducts are obtained, although in low yields. In protic medium β-adducts are formed in high yields by fast protonation of the more stable α-sulphonyl carbanion.

EXPERIMENTAL

Melting point are uncorrected. I.R. spectra were recorded in nujol on a Perkin Elmer 297 double beam spectrophotometer. N.M.R. spectra were recorded in $CDCl_3$, with TMS as internal standard, on a JEOL JNM-C-60 HL spectrometer. Silica gel G(Merck-Stahl) has been used for TLC with 9:1 benzene/acetone as eluent; column chromatographies were run on silica gel (Merck, 70-235 mesh ASTM), with the same eluent.

Reactions of pyrrolidin-1-yl-4-t-butyl cyclohexene with (E)- and (Z)-methyl-β-styryl sulphone.

A. Without solvent. Neat enamine (5.0 g, 24.1 mmol) and (E)-sulphone[2] (4.39 g, 24.1 mmol) were heated at 80°C for 24 h. The reaction mixture was then dissolved in CH_3CN (25 ml) and hydrolyzed with 10% HCl (15 ml) for 12 h at room temperature.
Dilution with water and extraction with chloroform gave a crude oil (8.0 g). TLC analysis showed, by comparison with authentic samples obtained by the reaction of the same enamine in CH_3CN[4], the presence of 4-t-butylcyclohexanone, (E)-methyl-β-styryl sulphone, three diastereoisomeric β-adducts ((2R*,αR*)-cis-2-|α-phenyl-β-(methylsulphonyl) ethyl|-4-t-butylcyclohexanone, (2S*,αR*)-trans-isomer and (2R*,αS*)-cis-isomer), and one or two α-adducts (cis-2-|α-(methylsulphonyl)-β-phenylethyl|-4-t-butyl cyclohexanones) (single spot). Column chromatography gave three fractions: the first consisted of 4-t-butylcyclohexanone and (E)-sulphone, the second consisted of the β-adducts and the third of the α-adduct(s). Yields are in table 2. The composition of the fractions was confirmed by N.M.R. and I.R. analysis.
B. In ethanol. Enamine (5.0 g, 24.1 mmol) and (E)-sulphone (4.39 g, 24.1 mmol) in dry ethanol (25 ml) were refluxed for 6 h. Hydrolysis and work up of the reaction mixture, as described above, gave only β-adducts (table 2).
Reactions with (Z)-sulphone[8] were carried out as described for the (E)-sulphone (table 2).

Reaction of pyrrolidin-1-yl-cyclohexene with (E)-methyl-β-styryl sulphone.

The reaction was carried out as described for (Z)-sulphone[1]; results are in table 1. Products were identified by comparison with the authentic samples previously obtained.[1]

Reactions of pyrrolidin-1-yl-4-methyl-cyclohexene with (E)- and (Z)-methyl-β-styryl sulphone.

(Z)-sulphone (1.82 g, 10 mmol) and enamine (2.64 g, 15 mmol) in dry CH_3CN (40 ml) were heated at reflux for 24 h. Hydrolysis with 10% HCl and extraction with chloroform gave an oil. Three fractions were separated by column chromatography: the first consisted of 4-methylcyclohexanone, the second of (E)-methyl-β-styryl sulphone while the last (33%) was a mixture of four adducts (Found C, 65.2; H, 7.40. $C_{16}H_{22}O_3S$ requires C, 65.3; H, 7.53). This mixture was again separated by column chromatography in two fractions: the first one (31%) consisting of two α-adducts (two characteristic double doublets at 4.3 and 4.1 δ, assigned to the hydrogen adjacent to the sulphone group)[1], the second one (2%) of two β-adducts (no signals around 4 δ)[1]. Recrystallization of the mixture of α-adducts from ether, allowed a pure sample of the more abundant compound to be obtained; m.p. 103-5°C (from ethanol) I.R.: ν_{MAX} (cm^{-1}): 1694 (C=O stretching), 1300, 1290 and 1130 ($-SO_2-$ stretching). N.M.R. (δ): 1.05 (d,3H); 1.6-2.8(m,10H); 2.6(s,3H); 4.15 (dd,1H); 7.35 (m,5H).
Under the same conditions (E)-sulphone gave 5% of α-adducts and 1% of β-adducts.

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