## CONJUGATE ADDITION OF AMINES TO CHIRAL (E) AND (Z) VINYL SULFOXIDES, AN ENANTIOCONVERGENT AND KINETIC PROCESS

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Summary: The kinetically controlled conjugate addition of benzylamine to isomeric (E) or (Z) chiral vinyl sulfoxides affords the same major diastereo-meric adduct.

In 1971 Stirling<sup>1</sup> reported that the conjugate addition of piperidine to  $(S_R)$ (Z) propenyl p-tolyl sulfoxide A gave a diastereomeric mixture of adducts  $(C_SS_P)$  B and  $(C_PS_P)$  C  $(87:13)^2$  in which the former predominated.



Stirling demonstrated that these products arise from a kinetically controlled process<sup>2</sup>. Based on purely steric considerations the reactive conformation depicted in **A** was proposed in which the least sterically demanding group on sulfur, the lone electron pair, was eclipsed with the ß-methyl group. Nucleo-philic attack by amine then occurred from the least sterically demanding  $\pi$ -face, that is the  $\pi$ -face opposite the bulky tolyl group. The possibility of H-bonding between the amine NH and the oxygen of the sulfoxide moiety was also suggested<sup>1,2</sup>.

We have recently demonstrated the application of the intramolecular Stirling reaction to chiral alkaloid synthesis<sup>3,4</sup>. While the stereochemical outcome of these reactions with chiral (Z) vinyl sulfoxides could be simply explained in terms of a Stirling like reactive conformation that of chiral (E) vinyl sulfoxides could not be satisfactorily explained. These later reactions proceeded with poorer selectivity and either opposite or the same  $\pi$ -face selectivity to their (Z) counterparts. We suggest that the products from our studies arise via cyclization of an incipient amino anion rather than the free amine<sup>4</sup>. To avoid possible ring conformational effects, which may influence the stereochemical outcome of the intramolecular reactions and probe solely the influence of the substituents at sulfur on the diastereo-selectivity of these reactions, it seemed important to examine the intermolecular reactions of isomeric (E) and (Z) (S<sub>R</sub>) chiral vinyl sulfoxides with amines. The chiral (S<sub>R</sub>)  $\beta$ -styryl p-tolyl sulfoxides 1a and 1b and (S<sub>R</sub>) 4-phenyl-1-butenyl p-tolyl sulfoxides 1c and 1d were prepared from  $\beta$ -bromo-

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styrene (E/Z = 85/15) and (1R, 2S, 5R) (-)-Menthyl(S)-p-toluenesulfinate and (+)-(R)-dimethylphosphorylmethyl p-tolyl sulfoxide and 3-phenylpropanal respectively according to literature procedures<sup>5,6</sup>.

The chiral vinyl sulfoxides 1(a-d) were treated with benzylamine in polar protic and non-polar aprotic solvent at  $80^{\circ}$  according to Table 1. Not unexpectantly the  $\beta$ -styryl sulfoxides 1(a,b) were much less susceptible to nucleophilic addition than their less conjugated counterparts 1(c,d). Quite surprisingly the individual reactions of 1a and 1b with benzylamine proceeded with similar diastereoselectivities and both gave 2a as the major diastereomeric product. The individual reactions of 1c and 1d with benzylamine were also enantioconvergent and yielded 2c as the major diastereomer.

The absolute configuration of 2c was established by reduction of diastereomerically pure 2c over Raney Nickel<sup>7</sup> to give (R)(+) N-benzyl-4-phenyl-2butylamine (Hydrochloride had  $[\alpha]_D^{15}$  + 6.6° (c 0.05, MeOH), lit<sup>8</sup> (S)(-) enantiomer. HCl,  $[\alpha]_D^{21}$  -7.4° (c 5.7, MeOH)). The analogous reaction of a mixture of 2a and 3a (5:1) gave (R)(+) N-benzyl-1-phenylethylamine ( $[\alpha]_D^{25}$  + 23.7° (c 0.136, EtOH), lit.<sup>9</sup>  $[\alpha]_D^{20}$  + 56.2° (c 1.071, EtOH)).

When chromatographically purified and diastereomerically pure 2c or 3c were individually re-exposed to the reaction conditions (benzylamine (5 equiv), EtOH,  $80^{\circ}$ , 2.5 days) they were returned  $\geq 98$  diastereomerically pure (<sup>1</sup>H-NMR (400 MHz) analysis). This result suggested essentially no (<2%) interconversion between 2c and 3c during the course of the conjugate addition reactions. Careful monitoring of the reactions of la and lb with benzylamine by  $^{1}$ H-NMR (400 MHz) indicated some interconversion (1-2%) between (E) and (Z) vinyl sulfoxides, however the (E) to (Z) ratio remained essentially constant as did the diastereoselectivity during the course of these reactions. A similar amount of isomerization (1-2%) was also noted when pure 1a was simply heated at 80° in pure benzene. In the case of the reaction of vinyl sulfoxides 1 (c or d) in benzene a few percent (<2%) of the (E)  $\beta-\gamma$  isomer of 1 could also be detected after 2.5 days. Stirling<sup>2</sup> has demonstrated that analogous allylic sulfoxides undergo rearrangement to the sulfenate and then allylic alcohol at a much faster rate than conversion to (E) or (Z) vinyl sulfoxides. When in a competitive experiment a 1:1 mixture of 1a and 1b was treated with benzylamine then the former isomer was consumed four times more rapidly than the latter.

We have clearly demonstrated that 2 and 3 are formed irreversibly and that the extent of interconversion between (E) and (Z) vinyl sulfoxide isomers is small (1-2) and can be readily accounted for by thermal isomerization. The possibility that in the reaction of (E) vinyl sulfoxides 1b and 1d with benzylamine that a significant amount of 3b(3d) arises from the reaction of the more reactive (Z) isomer (1a or 1c, respectively) seems unlikely because of the small extent of (E) to (Z) isomerization and the less than dramatic rate differences between 1a and 1b towards reaction with benzylamine.





Table 1. Reaction of 1 with benzylamine (3 molar equiv) at 80°, concentration 0.25 M

Vinyl	R <sub>1</sub>	R <sub>2</sub>	Time	Solvent	Yield	Ratio <sup>a</sup>
sulfoxid	e		(days)		(%)	2:3
1a	Ph	Н	7	Etoh	64 <sup>b</sup>	86:14
1b	н	Ph	7	Etoh	16 <sup>b</sup>	12:88
			12	Etoh	31 <sup>b</sup>	13:87
			20	EtOH	53 <sup>b</sup>	13:87
1c	PhCH <sub>2</sub> CH <sub>2</sub>	н	2	EtOH	2c(60) <sup>C</sup>	79:2
					3 <b>c</b> (16) <sup>C</sup>	
1c	PhCH <sub>2</sub> CH <sub>2</sub>	н	10	PhH	100 <sup>b</sup>	74:26
1d	н	PhCH <sub>2</sub> CH <sub>2</sub>	2	EtOH	2d(12) <sup>C</sup>	18:82
					3d(77)c	
1d	н	PhCH <sub>2</sub> CH <sub>2</sub>	10	PhH	100 <sup>b</sup>	45:55

<sup>a</sup> Determined by <sup>1</sup>H-NMR (400 MHz); <sup>b</sup> conversion as determined by <sup>1</sup>H-NMR (400 MHz), relative to starting vinyl sulfoxide; <sup>C</sup> Isolated yield from PTLC

It is apparent that (E) and (Z) vinyl sulfoxides adopt different reactive conformations in their reactions with amines. Clearly the transition state conformation 1 proposed by Stirling, which adequately explains the stereochemical outcome of the reaction of (Z) vinyl sulfoxides with amines, cannot be extrapolated to the reactions of (E) vinyl sulfoxides. Recent studies by Koizumi<sup>10</sup> on the conformational preference of vinyl sulfoxides bearing dipolar substituents suggest that in solution (E) and (Z) vinyl sulfoxides favour the <u>s-cis</u> (S=O and C=C <u>syn</u> coplanar) and <u>s-trans</u> (S=O and C=C <u>anti</u> coplanar) conformations respectively. The stereochemical outcome of our reactions in ethanol can be readily accounted for by inferring nucleophilic attack by amine on the <u>s-cis</u> 4 and <u>s-trans</u> 5 conformations of **1b(1d)** and **1a(1c)** respectively from the least hindered  $\pi$ -face (ie, <u>anti</u> to tolyl).



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For (E) vinyl sulfoxides in non-polar solvent, where the sulfoxide oxygen would be poorly solvated, little difference in free energy would be expected between conformations 1 ( $\beta$ -H and sulfoxide electron pair eclipsed) and 4 ( $\beta$ -H and oxygen of sulfoxide eclipsed). The poor diastereoselectivity observed for the reaction of (E) 1d in benzene is consistent with this expectation.

Furthermore the independence of the diastereoselectivity of (Z) vinyl sulfoxide 1c on solvent polarity is also consistent with reaction via conformation 5 in which the polar sulfoxide oxygen is remote from the site of conjugate addition.

While reactive conformations different to 1, 4 and 5 based on stereoelectronic considerations, have been suggested for the addition of amino anions<sup>4</sup> and carbanions<sup>11,12</sup> to chiral vinyl sulfoxides, the transition state structure for anionic addition probably correlates poorly with that for amine addition. Whether these ground state conformations bear any relationship to the actual reactive conformation awaits further kinetic and theoretical<sup>13</sup> investigations.

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## Acknowledgement

Financial support by the Australian Research Grants Scheme and Johnson and Johnson Development Research Corporation Limited, Australia is gratefully acknowledged.

(Received in UK 10 February 1988)