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THE SYNTHESIS AND STRUCTURE OF β-ENAMINO SULPHOXIDES

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Abstract - Parent aliphatic and aromatic β-enamino sulphoxides bearing secondary and tertiary alkylamino residues are synthesized by mixing of alkylamine hydrochlorides with metallated enolates of the β-oxosulphoxides in methanol. The latter compounds are obtained in very good yields from metallated sulphoxides and tertiary amides at room temperature in tetrahydrofuran. The majority of the products have enaminic structures in chloroform solution, and E and Z configurations with tertiary and secondary β-alkylamino residues, respectively.

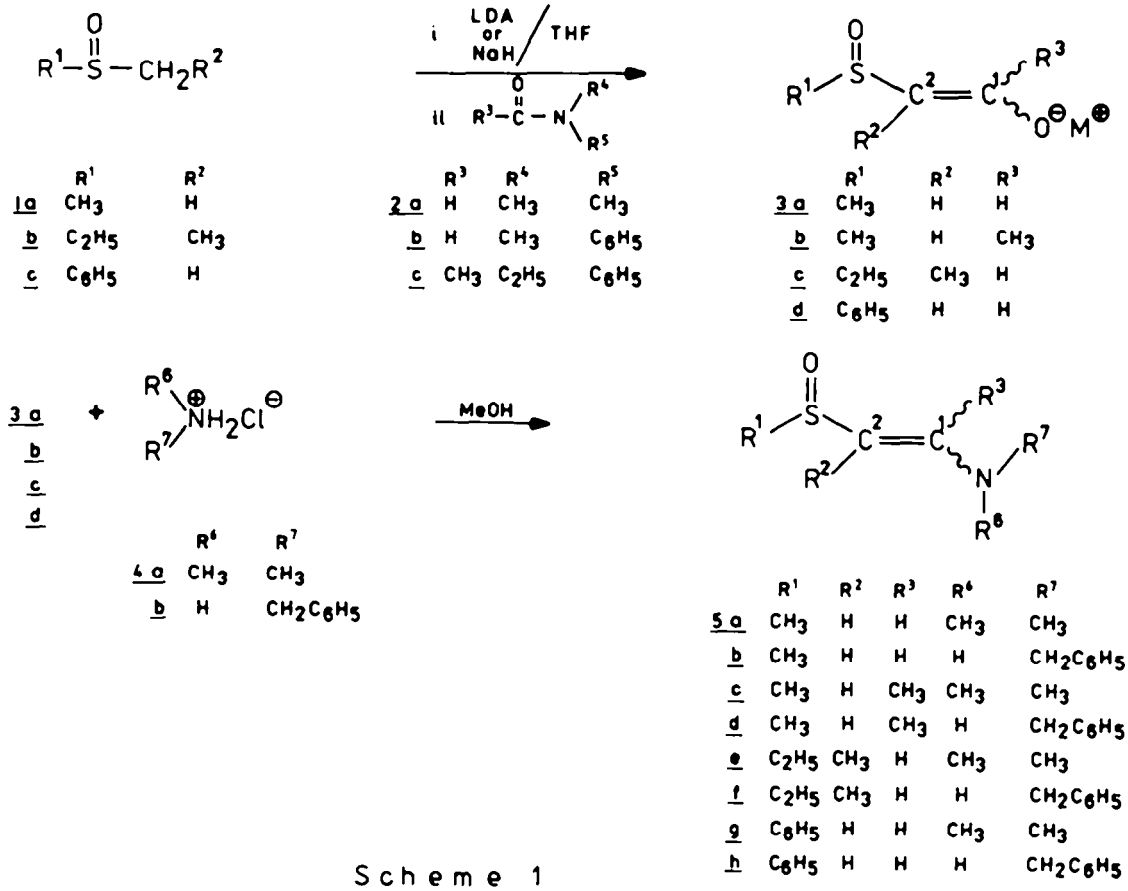
The chiral sulphoxide group has recently attracted much of interest for use in asymmetric synthesis[1,2], especially for stereoselective transformations utilizing commercially available (-)menthyl (S)-toluene-p-sulphinate as starting material. Methods for obtaining other simple but reactive sulphoxide group containing synthons are desirable. One such possibility is visualized by β-sulphinyl enamines of yet unknown chemistry, of which the synthetic potential, due to the presence of a chiral center, can be even greater than that of nitroenamines[3] or enaminones[4].

Our interest in the chemistry and spectroscopy of activated enamines[5,6,7] prompted us to investigate the title problem, all the more that to the best of our knowledge in only one instance has a synthesis of parent alkyl β-sulphinyl enamines been reported. This was achieved by the addition of primary and secondary amines to acetylenic and allenic sulphoxides[8,9]. More recently, an efficient stereospecific synthesis of the β-enamino and β-imino sulphoxides was reported based on reaction of lithioenamines with commercially available optically pure sulphinate ester[10]. A few other procedures have been published for obtaining the abovementioned tautomers with activating groups such as thioalkyl, phenyl or cyano at the olefinic carbon atom; namely, α-thioalkyl-β-enamino sulphoxides from metallated methyl thiomethylsulphoxides and nitriles[11], β-phenyl-β-imino sulphoxides from α-lithiomethylsulphoxides with nitriles[12] and α-cyano-β-iminosulphoxides from nitriles and sulphinic ester with lithium diisopropylamide[13].

RESULTS AND DISCUSSION

In our novel approach the reaction of metallated simple dialkyl or diaryl sulphoxides with tertiary amides followed by addition of the amine hydrochloride yields, in a one pot synthesis, a variety of parent alkyl or phenyl, β-enamino sulphoxides (see Scheme 1, Tables 1,2).

Various amides can be used effectively to produce intermediate 3 in high yields, as shown in Scheme 1 and Table 1, although a lower yield was obtained with N-ethyl-N-phenylacetamide. It should be pointed out that the use of the amides allows obtaining (β-alkylunsubstituted-)β-enamino sulphoxides 5 while we failed trying to synthesize them using formyl ester according to Corey's procedure[14]. When our work was in progress G. Solladié et al.[15] published the procedure with α,β-unsatura-



	R^1	R^2
1a	CH_3	H
b	C_2H_5	CH_3
c	C_6H_5	H

	R^3	R^4	R^5
2a	H	CH_3	CH_3
b	H	CH_3	C_6H_5
c	CH_3	C_2H_5	C_6H_5

	R^1	R^2	R^3
3a	CH_3	H	H
b	CH_3	H	CH_3
c	C_2H_5	CH_3	H
d	C_6H_5	H	H

3a, b, c, d +

	R^6	R^7
4a	CH_3	CH_3
b	H	$CH_2C_6H_5$

	R^1	R^2	R^3	R^6	R^7
5a	CH_3	H	H	CH_3	CH_3
b	CH_3	H	H	H	$CH_2C_6H_5$
c	CH_3	H	CH_3	CH_3	CH_3
d	CH_3	H	CH_3	H	$CH_2C_6H_5$
e	C_2H_5	CH_3	H	CH_3	CH_3
f	C_2H_5	CH_3	H	H	$CH_2C_6H_5$
g	C_6H_5	H	H	CH_3	CH_3
h	C_6H_5	H	H	H	$CH_2C_6H_5$

Scheme 1

Table 1 Synthesis of the enolates 3

Enolate	Amide	Method	Yield %[a]
3a	2a	A	98
	2a	B	10
	2b	B[b]	97
3b	2c	B[b]	38
3c	2a	A	95
3d	2a	A	83

a Yields are calculated basing on the amount of the salt obtained after work up and drying it in high vacuum. The identity of the products was checked by 1-H and 13-C NMR.
b Reaction mixture was additionally kept at boiling temperature for two hours.

ted imidazolide to obtain β-keto sulphoxides, which further confirms the generality of our prosech.

Since salts 3 readily precipitate from the reaction mixture, the second step, i.e. amination of the β-carbon in 3, can be performed on an isolated salt or in a one-pot by adding methanol. One should note that the amination of the salts 3 with arylamine hydrochlorides to obtain arylamino derivatives[16] of 5 failed.

The alkyl-β-enamino sulphoxides are yellow nondistillable, highly hygroscopic, difficultly cristallizable oils which show contamination with decomposition products after a month standing in chloroform solution; their characterization by elemental analysis is difficult (comp. ref. 8) on account of their hygroscopic properties. ^1H NMR and MS spectra were used to assign the structure unambiguously (Table 3, Table 4).

All the sulphoxides studied exist, in chloroform solution, only in the enamine form, as evidenced by ^1H NMR chemical shifts, with the exception of compound 5d which showed, in ^1H NMR, two sets of signals attributable to the enamine (ca. 60 %) and the imine forms. The assignment of the composi-

Table 2 Reaction conditions for synthesis and purification of the β-enamino sulphoxides 5

No.	Amine hydrochloride	Method	Reaction conditions	Chromatography on Al_2O_3 base Eluent C_6H_6/MeOH/Et_3N ml	Yield[a] %	M.p. °C
5a	4a	C	MeOH, room temp.	$CHCl_3$	30	-
5b	4b	C	MeOH, room temp.	b	46	106-114(C_6H_6)
5c	4a	D	1. MeOH, 0°C 2. Et_2O/C_6H_6, 0°C	c	72[d]	-
5d	4b	D	1. MeOH, room temp. 2. boiling C_6H_6	100/2/2	46	105-117
5e	4a	C	MeOH, 0°C	150/5/2	39	-
5f	4b	C	MeOH, room temp.	150/10/4	34	-
5g	4a	C	MeOH, 0°C	50/50/2[e]	35	90-92
5h	4b	D	1. MeOH, room temp. 2. boiling C_6H_6	120/2/2	22	124-128

a Unless otherwise indicated the yields are calculated basing on the product obtained after chromatography.
b Product crystallized from the oil obtained after work up.
c The attempts to chromatograph the product on alumina base failed. The only impurity was β-ketosulphoxide removed by amination with excess amine.
d Based on the amount of the crude product obtained.
e Chloroform was used instead of methanol.

Table 3 ^1H NMR chemical shifts, δ(ppm), and coupling constants, J(H,H) Hz, in β-enamino sulphoxides 5[a]

	R^1	R^2	R^3	R^6	R^7	R^1	R^2	R^3	R^6	R^7
5a	CH_3	H	H	CH_3	CH_3	2.67	5.10(13.5)	6.97(13.5)	2.93	2.93
5b	CH_3	H	H	H	$CH_2C_6H_5$	2.55	5.20(13.5)	6.93(13.5) (8.3)	5.20	4.12(5.3)-CH_2;7.16-C_6H_5
5c[b]	CH_3	H	CH_3	CH_3	CH_3	2.66	4.97	2.24	2.96	2.96
						2.74	4.92	2.14	2.66	2.66
5d[c]	CH_3	H	CH_3	H	$CH_2C_6H_5$	2.54	5.05	2.17	5.67	4.19(4.8)-CH_2;7.40-C_6H_5
						2.64	3.72(CH_2)	2.08	-	4.58-CH_2;7.40-C_6H_5
5e[d]	C_2H_5	CH_3	H	CH_3	CH_3	1.06(7.2) 2.51(7.2)	1.94	6.42	3.00	3.00
5f	C_2H_5	CH_3	H	H	$CH_2C_6H_5$	1.01(7.6) 2.67(7.6)	1.75	6.71(13.5)	5.17 (13.5)	4.24(6.7)-CH_2;7.33-C_6H_5
5g	C_6H_5	H	H	CH_3	CH_3	7.44-7.89	5.08(13.5)	7.12(13.5)	2.87	2.87
5h	C_6H_5	H	H	H	$CH_2C_6H_5$	7.13-7.73	5.20(13.5)	7.13-7.20[e]	5.86	4.16(5.4)-CH_2;7.13-7.73-C_6H_5

a The spectra were recorded from $CDCl_3$ solutions with internal TMS.
b Mixture of the E- and Z- isomers, upper and lower set, respectively, see text.
c Mixture of enamino (upper set) and imino (lower set) tautomers, see text.
d The spectrum was recorded in CCl_4 solution.
e Signal obscured by aromatic proton resonances.

tion is unambiguously confirmed by the ^{13}C chemical shifts: most characteristic being those of the $-C^1=N$ (162.8 ppm) and SOC^2H_2 (65.0 ppm) atoms in the imine and 153.7, 98.0 ppm in the enamine, respectively. Our assignment in 5d is in contradiction to the assignment made by Stirling et al.[8] in a compound closely related to 5d ($R^1 = CH_2C_6H_5$) which is claimed to exist in $CDCl_3$ solution as a 4:1 mixture of the Z- and E- isomers. Apparently, the tautomeric composition is sensitive to structural features influencing the basicity of the nitrogen atom. The relevant example is that of the recently published sulphoxide of structure 5 (R^1= p-tolyl, R^7= t-butyl)[15] claimed to exist as a 3:1 mixture of the enamine and the imine forms, in contrast to the structurally similar compound 5g (R^1= phenyl, $R^7 = CH_2C_6H_5$) which in chloroform shows only one set of signals assigned to the enamine structure by ^1H and ^{13}C NMR.

Tertiary (β-alkylunsubstituted) β-enamino sulphoxides exist in chloroform solution in E form al-

Table 4 Mass spectrometry of the β-enamino sulphoxides 5[a]

5a	M^+ = 133(46.7), 118(100), 117(10.7), 116(4.7), 102(16.8), 101(36.5), 100(75.1), 88(11.1), 70 (18.5), 69(11.1), 68(17.1), 55(19.9), 44(41.2), 42(75.9).
5b	M^+ = 195(1.9), 180(8.3), 132(11.0), 131(12.8), 118(1.8), 106(14.3), 91(100), 78(28.8), 65(12.0), 51(11.2).
5c	M^+ = 147(14.6), 132(42.1), 116(6.6), 115(17.0), 114(31.3), 84(12.9), 71(57.2), 70(43.2), 63 (55,9), 56(95.9), 43(100), 42(77.4).
5d	M^+ = 209(0.8), 194(5.8), 146(16.2), 145(23.3), 130(3.4), 104(26.8), 91 (100), 65(14.5).
5e	M^+ = 161(22.0), 145(3.6), 132(96.6), 116(18.5), 115(51.3), 114(100), 84(13.9), 82(23.5), 68(28.0), 44(36.5), 42(81.6).
5f	M^+ = 223(1.3), 194(11.2), 146(7.6), 145(8.3), 135(14.1), 119(24.7), 117(23.6), 91(100), 77 (12.9), 65(15.8), 43(18.2).
5g	M^+ = 195(3.3), 179(3.4), 178(4.4), 147(100), 146(22.8), 132(8.8), 118(15.4), 101(15.9), 100 (29.8), 91(18.8), 86(5.3), 77(17.6), 70(15.2), 55(18.1), 51(16.6), 42(45.0).
5h	M^+ = 257(0.3), 209(8.4), 132(4.4), 91(29.7), 78(100), 77(24.6), 52(20.7), 51(21.8), 50(17.6).

a Fragmentation data, m/z and intensities (in brackets), were taken from 70eV experiment.

though compound 5c exist as a 4:1 mixture of the E- and Z- isomers. Secondary enaminosulphoxides show, in chloroform solution, only one set of signals assigned to the Z- isomer. The stereochemical assignment in the two series was also investigated by running NOE experiments on compounds 5e and 5f. Weak irradiation of the C^2-CH_3 group in 5f led to a 12% increase in intensity for the C^1-H proton, while under the same experimental conditions irradiation of the C^2-CH_3 in 5e had no effect on the intensity of the C^1-H proton.

It should be noted that the olefinic $^3J(H,H)$ coupling constant is not sensitive to geometrical isomerism, since in both isomers it amounts to 13.5 Hz. Furthermore, the resonances of N-H protons in the Z-isomer, supposed to be hydrogen-bonded, appear at 5.2 - 5.89 ppm and are shifted considerably to lower frequencies as compared to the structurally related enaminones[17] (δ = 9 ppm). Because of these ambiguities further spectroscopic studies are being carried out to determine the stereochemistry of the products 5.

EXPERIMENTAL

Synthesis of Enolates 3a - 3d

Method A

An equimolar amount of n-butyllithium was added dropwise at -40°C to diisopropylamine (37.5 mol) in 15 ml of tetrahydrofuran and stirred for 0.5 h at -10°C. The sulphoxide (37.5 mol) was then added at -10°C and the reaction mixture was stirred for one hour. An equivalent of dry amide was added slowly while raising the temperature to 25°C and stirring for another hour. The reaction mixture was left overnight and the precipitated yellow solid was filtered off and washed with ether.

Method B

To the suspension of NaH (104 mmol scale) in dry tetrahydrofuran was added an equimolar amount of dry dimethylsulphoxide and the reaction mixture was heated at 67°C for two hours. After cooling to room temperature the equivalent of amide was added and the reaction was worked up as in method A.

Synthesis of the β-Enamino Sulphoxides 5

Method C

Typically, 5.75 mmol of the salt 3 and 6.1 mmol of amine hydrochloride were dissolved in methanol and stirred for two hours (see Table 2). After evaporation of solvent the resulting oil was dissolved in benzene/methanol mixture and dried with potassium carbonate. After filtration and evaporation the crude product was chromatographed on basic alumina using a mixture of benzene, methanol and triethylamine as eluent (see Table 2).

Method D

The crude product obtained by method C and tested by NMR for the presence of appreciable amount of unreacted β-oxosulphoxide, was additionally aminated with the excess of appropriate amine in a presence of the catalytic amount of p-toluenesulphonic acid over molecular sieves 3A (for details see Table 2). The solution was dried with potassium carbonate and filtered, solvent and excess of amine were evaporated and resulting oil was chromatographed as in method C.

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