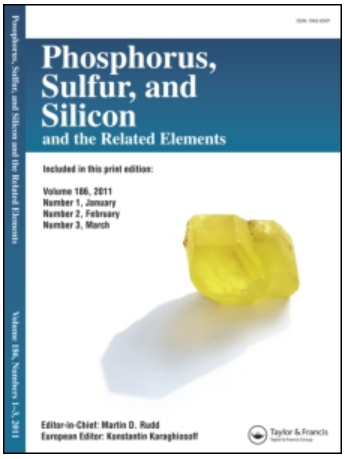

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AMBIDOSELECTIVITY OF THE ENETHIOLATES REACTION WITH ELECTROPHILES: THE CASE OF EPOXIDES

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AMBIDOSELECTIVITY OF THE ENETHIOLATES REACTION WITH ELECTROPHILES: THE CASE OF EPOXIDES

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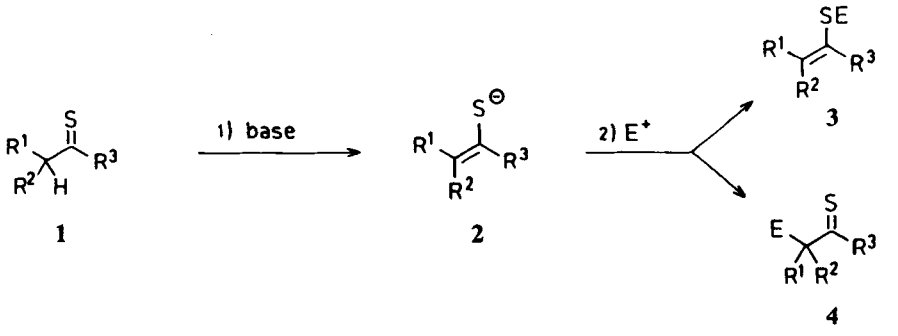
Lithium enethiolates, generated by deprotonation of various thiocarbonyl compounds, have been submitted to the reaction of epoxides. These ambident nucleophiles react on sulfur to afford (2-hydroxyalkyl) vinyl sulfides. Various thiocarbonyl compounds have been used: dithioesters, thionesters and thioketones. Compilation of literature dealing with the ambidoselectivity of the enethiolates reaction with electrophiles confirms the following trend: alkylation occurs on sulfur whereas addition on π systems occurs on carbon.

INTRODUCTION

Enethiolates (**2**) are ambident nucleophiles which frequently differs in behaviour from their oxygen analogues.[1-5] They are usually prepared by deprotonation of thiocarbonyl compounds (**1**). Their reactions with electrophiles have been recently reported to occur on both nucleophilic centers (Scheme 1):

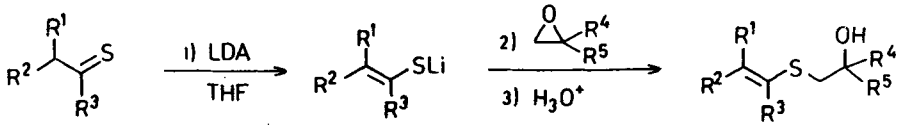
-reaction with alkyl halides,[1-5] carboxylic acid halides,[1-5] acid anhydrides,[1-5] trimethylchlorosilane,[6] sulfenylating agents,[7] phosphorus chlorides[8] and carbon disulfide[9] takes place on sulfur to yield vinyl sulfides (**3**).

-reaction with aldehydes and ketones,[10-13] unsaturated ketones[14-18], and carbon oxysulfide[9] occurs on carbon to afford thiocarbonyl derivatives (**4**).



SCHEME 1

*Author to whom all correspondence should be addressed.



SCHEME 2

The orientation can depend upon the reaction conditions: in some cases[7,15] products (**3**) from kinetic reactions on sulphur have been transformed *via* equilibration to the thermodynamically more stable carbon products (**4**).

A case of borderline reactivity[17] revealed that lithium thioenolates from thioketones have a marked tendency to *S*-ambidoselectivity as compared to those from other thiocarbonyl compounds: dithioesters, thionesters and thioamides which give *C*-selectivity in this case.

The recent developments of the chemistry of carbanions and enolates towards epoxides[19-21] prompted us to study the reactivity of thioenolates. No extensive study has been reported. The only precedent is due to Reglier and Julia[22] who used recently the *S*-alkylation of an enethiolate by ethylene oxide to convert a vinyl sulfide into the corresponding aldehyde.

We have prepared the lithium enethiolates by deprotonation of various thiocarbonyl compounds with LDA in THF and submitted them to the action of epoxides under aprotic conditions. The reaction could be carried out with dithioesters, thionesters and thioketones at temperatures in the range of $-10°C$ to room temperature (Table I). The structure of (2-hydroxyalkyl) vinyl sulfide may be readily assigned to the products (**5**)-(**13**) from their ^1H and ^{13}C NMR and IR spectra (Scheme 2).

Yields are quantitative. The selectivity of this reaction is high: no other compound was detected on the NMR spectrum. The purification of these sensitive products is therefore unnecessary. Use of classical separation techniques resulted in partial loss or transformation of the hydroxy vinyl sulfides (Table I). Chromatography of compounds (**5**) and (**6**) on silica gel or treatment of (**6**) with a catalytic amount of *para*-toluene sulfonic acid initiated cyclization[22] to give oxathiolanes (**14**) and (**15**). This reaction occurs *via* proton addition on the ketene dithioacetal moiety to give a stabilized dialkylthiocarbonium ion which is trapped intramolecularly by the hydroxyl group.

The reaction with propene oxide occurred exclusively on the less substituted carbon of the 3-membered ring. We have also attempted the reaction of di*iso*propyl thioketone with butadiene monoepoxide. Though the reaction is not regioselective, the NMR spectrum shows that the major product is a secondary alcohol and thus arises from SN_2 and not SN_2' alkylation.

The following limitations have emerged:

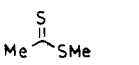
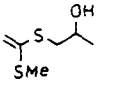
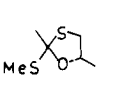
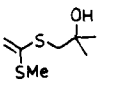
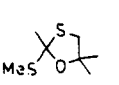
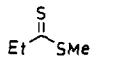
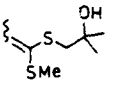
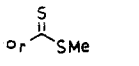
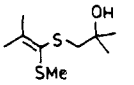
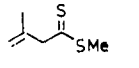
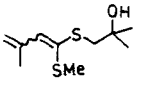
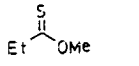
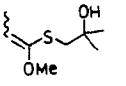
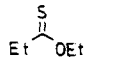
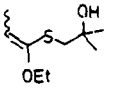
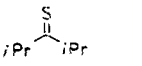
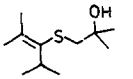
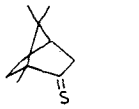
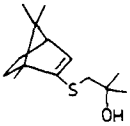
–at room temperature, thioenolates are unreactive towards styrene oxide and more sterically hindered oxiranes such as *trans* 2-butene oxide, limonene oxide and β-pinene oxide.

–no reaction was observed with *N*,*N*-dimethyl thioacetamide.

Thus, thioenolates are moderately reactive with epoxides. Under kinetic condi-

TABLE I

Reaction of lithium enethiolates with epoxides

Thiocarbonyl compound	Epoxide	Reaction temp °C	conditions time	Product		Product after chromatography	
		−10	20 min		(5)		(14)[1] 30%
"		−10	20 min		(6)		(15) 50%
	"	−10	2 hr		(7)[2]		
	"	20	72 hr		(8)		(8) 68%
	"	−10	3 hr		(9)[3]		
	"	20	48 hr		(10)[4]		
	"	20	72 hr		(11)[5]		
	"	−10	20 min		(12)		
	"	20	24 hr		(13)		(13) · 46%

[1] Mixture of cis and trans isomers (40 : 60).
[2] Mainly one isomer.
[3] Mixture of Z and E isomers (ratio undet).
[4] Mixture of Z and E isomers (72 : 28).
[5] Mixture of Z and E isomers (55 : 45).

tions the reaction is ambidoselective on the sulphur atom, whatever the nature of the starting thiocarbonyl compound is.

Compilation of our results and the miscellaneous literature reports leads to the following rule:

–reaction of enethiolates with alkylating and heteroalkylating agents occurs on sulfur.

–addition to electrophiles bearing π-bonds (C=O, C=C) takes place on carbon. Some exceptions may be found, which can be explained by sterical hindrance[16] of the carbon site of the enethiolate or by particular electronic factors.[9,17,23]

EXPERIMENTAL

Thiocarbonyl compounds have been prepared by following methods:
–dithioesters by reaction of alkyl-magnesium halides with carbon disulfide and alkylation[24–26]
–thionesters by reaction of propionitrile with alcohols and treatment with hydrogen sulfide[27]
–thioketones by reaction of ketones with hydrogen sulfide and orthoformate in acidic medium[28,17]
Reactions have been carried out under a positive nitrogen pressure in a glass vessel equipped with rubber septa.

Preparative liquid chromatography has been realized at medium pressure (5–7 bars) with a Jobin Yvon Chromatospac Prep. 10 equipped with a refraction detector. Columns have been prepared by compressing a suspension of 100 g of 60 H Merck TLC silicagel in the eluting solvent. NMR spectra have been recorded in the following conditions: ^{1}H with Varian EM 360 at 60 MHz; ^{13}C with Bruker WP 60 at 15.8 MHz.

General procedure. The thiocarbonyl compound (2–6 mmol) is added dropwise to a solution of LDA (1 equivalent) in anyhdrous THF cooled at −78°C. The mixture is stirred during 10 min (1 hr in the case of methyl but-3-endithioate). The epoxide (1–2 equivalents) is added dropwise. The reaction temperatures and times are indicated in the table. The mixture is quenched by an ammonium chloride solution and extracted by partition between ethyl ether and brine. The organic layer is dried on magnesium sulfate. Evaporation of the solvent furnishes the (2-hydroxy alkyl) vinyl sulfides **5**–**13** as oils. Yields are quantitative (purity > 90%).

1-(2-hydroxypropylthio)-1 methylthioethylene **5**. ^{1}H NMR (CCl_4): 1.20 (d; J = 6 Hz; Me); 2.25 (s; SMe); 2.8 (m; SCH_2); 5.02 and 5.25 (2 s; CH_2=). ^{13}C NMR (C_6D_6): 16.7; 28.2; 46.8; 71.3; 112.4; 142.3. IR (CCl_4): 3600 cm^{-1} (OH). Anal. Calcd for $C_6H_{12}OS_2$: C, 43.90; H, 7.32. Found: C, 43.96; H, 7.20. Mass spectrum: m/e 43 (94%); 59 (25%); 75 (46%); 107 (16%); 117 (100%); 149 (2%); 164 (2%).

2,4-Dimethyl-2-methylthio-3,1-oxathiolans cis and trans **14**. Column chromatography of compound **5** on silica gel with a 90 : 10 mixture of cyclohexane and ethyl acetate accomplishes cyclization to give a 40 : 60 mixture of isomers **14**. Yield: 30%. ^{1}H NMR (CCl_4): 1.30 (d; J = 10 Hz; Me-4 of the major isomer); 1.40 (d; J = 8 Hz; Me-4 of the minor isomer); 1.85; 2.08; 2.29 (3 s; Me-2 and SMe of both isomers); 2.5–3.5 (CH_2-5 and CH-4). ^{13}C NMR ($CDCl_3$): 14.1; 28.2; 28.6; 30.9; 45.8; 89.0; 100.0.

1-(2-Hydroxy-2-methylpropylthio)-1-methylthioethylene **6**. ^{1}H NMR (CCl_4): 1.22 (s, 2Me); 1.82 (s; OH); 2.28 (s; SMe); 2.90 (s; SCH_2); 5.2 and 5.5 (2 s; CH_2=). ^{13}C NMR (C_6D_6): 16.8; 28.7; 47.4; 70.9; 112.3; 143.6. IR (neat): 3460 cm^{-1} (OH). Anal. Calcd for $C_7H_{14}S_2O$: C, 47.19; H, 7.80. Found: C, 47.20; H, 7.92. MS: 43 (100%); 55 (45%); 59 (46%); 61 (35%): 73 (30%); 75 (32%); 89 (46%); 131 (57%); 178 (12%).

2,4,4-Trimethyl-2-methylthio-3,1-oxathiolan **15**. Column chromatograpy of compound **6** on silica gel with a 80 : 20 mixture of cyclohexane and ethyl acetate accomplishes cyclization to give product **15**. Yield: 50%. ^{1}H NMR: 1.30 and 1.46 (2s; Me-4); 1.84 (s; Me-2); 2.10 (s; SMe); 2.90 and 3.37 (AB; J = 11 Hz; SCH_2). ^{13}C NMR ($CDCl_3$): 14.1; 28.2; 28.5; 30.9; 45.7; 89.0; 100.1.

1-(2-Hydroxy-2-methylpropylthio)-1-methylthiopropene **7**. Only one isomer (probably Z[29]) is clearly discernable by NMR. ^{1}H NMR (CCl_4): 1.20 (s, 2Me—COH) 1.92 (d; J = 6 Hz; Me—CH=); 2.18 (s; SMe); 2.83 (s; SCH_2); 5.96 (q; J = 6 Hz; =CH). ^{13}C NMR (C_6D_6): 16.5; 16.8; 28.6; 46.4; 71.2; 130.8; 133.9. IR (CCl_4): 3470 cm^{-1} (OH). MS: 41 (32%); 43 (53%); 45 (80%); 47 (26%); 59 (89%); 71 (60%); 72 (36%); 87 (100%); 134 (31%); 192 (32%).

1-(2-Hydroxy-2-methylpropylthio)-2-methyl-1-methylthiopropene **8**. ^{1}H NMR (CCl_4): 1.18 (s; 2Me—COH); 2.00 and 2.04 (2 s; Me_2C=); 2.13 (s; SMe); 2.48 (s; OH); 2.82 (s; CH_2). ^{13}C NMR ($CDCl_3$): 17.1; 23.9; 28.5; 46.6; 71.0; 125.6; 143.9. IR (CCl_4): 3460 cm^{-1} (OH). MS: 45 (17%); 59 (46%); 61 (20%); 71 (17%); 85 (58%); 86 (21%); 101 (100%); 148 (37%); 206 (40%). Column chromatography of compound **4** on silica gel with a 80 : 20 mixture of cyclohexane and ethyl acetate gives unchanged **4**. Yield: 68%.

1-(2-Hydroxy-2-methylpropylthio)-3-methyl-1-methylthio-1,3-butadienes Z and E **9**. ^{1}H NMR (CCl_4): 1.18 (s; 2Me—COH); 2.00 (s; Me—C=); 2.30 (s; SMe); 5.08 (m; $=CH_2$); 6.32 (m; =CH—). IR (CCl_4): 3500 cm^{-1} (OH). MS: 45 (27%); 59 (28%); 91 (44%); 98 (24%); 131 (25%); 138 (31%); 145 (100%); 203 (21%); 218 (2%).

1-(2-Hydroxy-2-methylpropylthio)-2-methyl-1-methoxypropenes Z and E **10**. Isomeric ratio (NMR) A/B = 72 : 28. ^{1}H NMR: 1.14 (s; 2Me-COH); 1.55 and 1.68 (2d; J = 7 Hz; Me—CH= of B and A); 2.57 and 2.70 (2s; SCH_2 of B and A); 3.44 (s; OMe); 4.68 and 5.00 (2q; J = 6 Hz; =CH of A and B). IR (CCl_4): 3540 cm^{-1} (OH). MS: 41 (40%); 43 (33%); 55 (60%); 57 (38%); 59 (100%); 71 (63%); 73 (60%); 88 (57%); 103 (27%); 118 (60%); 176 (57%).

1-Ethoxy-1-(2-hydroxy-2-methylpropylthio)propenes Z and E **11**. Isomeric ratio (NMR) A/B = 55 : 45. ^{1}H NMR (CCl_4): 1.59 and 1.81 (2d; J = 8 Hz; Me—CH= of B and A); 2.60 and 2.74 (2 s; SCH_2 of B and A); 2.9 (bs; OH); 3.78 and 3.90 (2q; J = 7 Hz; OCH_2 of A and B); 4.85 and 5.20 (q; J = 8 Hz; =CH of A and B). ^{13}C NMR ($CDCl_3$): 11.9; 13.4; 14.5; 14.8; 28.4; 44.3; 45.0; 64.8; 65.2; 70.9; 71.0; 102.3; 115.1; 148.9; 150.2. IR (neat): 3390 cm^{-1}. MS: 43 (21%); 55 (34%); 57 (100%); 59 (56%); 71 (20%); 73 (33%); 88 (25%); 104 (75%); 132 (110%); 190 (28%).

1-(2-Hydroxy-2-methylpropylthio)-1-isopropyl-2-methylpropene **12**. ^{1}H NMR (CCl_4): 1.04 (d; J = 7 Hz; 2Me of *i*Pr); 1.20 (s; 2Me—COH). 1.76 and 1.98 (2 s, Me_2C=); 2.6 (s; SCH_2); (m; CH of *i*Pr). ^{13}C NMR ($CDCl_3$): 20.7; 21.5; 24.0; 28.7; 32.4; 50.9; 70.7; 135.1; 137.6. IR (CCl_4): 3550 cm^{-1} (OH). MS: 41 (90%); 43 (55%); 55 (84%); 59 (100%); 81 (61%); 95 (11%); 96 (50%); 97 (48%); 129 (22%); 144 (23%); 202 (25%).

2-(2-Hydroxy-2-methylpropylthio)-2-bornene **13**. ^{1}H NMR (CCl_4): 0.70; 0.80; 0.98 (3s; Me-1 and 2 Me-7); 1.23 (s; 2Me—COH); 2.41 (t; J = 3 Hz; CH-4); 2.70 (s; SCH_2); 5.50 (d; J = 3 Hz; =CH). NMR ^{13}C ($CDCl_3$): 11.3; 19.6; 26.5; 28.7; 31.7; 44.9; 52.0; 56.2; 56.7; 65.8; 70.6; 124.7; 144.3. IR (CCl_4): 3560 cm^{-1}. MS: 41 (87%); 55 (67%); 59 (49%); 69 (40%); 81 (49%); 85 (45%) : 88 (41%); 95 (80%); 101 (68%); 108 (60%); 109 (51%); 168 (48%) 182 (100%); 240 (52%). Column chromatography of compound **13** on silica gel with a 80 : 20 mixture of cyclohexane and ethyl acetate gives unchanged **13**. Yield: 46%.

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