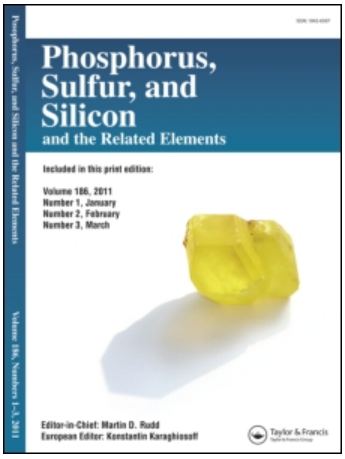

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Wladislaw, Blanka , Bjorklund, Marcelo B. , Marzorati, Liliana and Zukerman-schpector, Julio(2000) 'REACTIONS OF β-KETO SULFOXIDES WITH SULFUR ELECTROPHILES. PART II. STEREOCHEMICAL AND CONFIGURATIONAL STUDIES OF THE INTERMEDIATE ENOLATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 157: 1, 139 — 144
To link to this Article: DOI: 10.1080/10426500008040518
URL: http://dx.doi.org/10.1080/10426500008040518

Phosphorus, Sulfur and Silicon, 2000, Vol. 157, pp. 139-144
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REACTIONS OF β-KETO SULFOXIDES WITH SULFUR ELECTROPHILES. PART II. STEREOCHEMICAL AND CONFIGURATIONAL STUDIES OF THE INTERMEDIATE ENOLATES

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(Received Recevied May 19, 1999; In final form September 8, 1999)

Some β-keto sulfoxides containing different groups at the sulfinyl moiety were submitted to sulfenylation reaction employing two procedures: in homogeneous media and by PTC to give the corresponding monosulfenylated products. The Z configuration for the enolates of the β-keto sulfoxides independently of the group at the sulfur moiety is proved by ^{1}H NMR NOE difference experiments. The diastereoselectivity observed in the case of a t-butyl sulfinyl derivative is rationalized by preferred attack of the sulfur electrophile to the unhindered face of enolate not shielded by t-butyl group, as shown by X-ray analysis of the corresponding enol ether.

Keywords: Sulfenylation; keto-sulfoxides; Z-enolates; diastereoselectivity

INTRODUCTION

β-Keto sulfoxides, readily available by two alternative methods, namely acylation of α-sulfinyl carbanions or thiolation of α-halo ketones, followed by oxidation, have received much attention mainly due to the highly diastereoselective reductions which they undergo in their optically active form.[1] However, the presence of the acidic methylenic protons between the carbonyl and sulfinyl groups opens the possibility for reactions with a

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variety of electrophiles, leading to the formation of carbon-carbon and carbon-heteroatom bonds.

Early studies on alkylation of β-keto sulfoxides, employing as base NaH in DMSO or THF, showed that mono- and dialkylated derivatives can be obtained in good yields.[2,3] More recent investigations[4] indicated that the alkylation of β-keto sulfoxides can be performed by an ion-pair extraction method employing aqueous NaOH and tetrabutylammonium hydrogen sulphate, in dichloromethane. It was shown that the site of this reaction depends on the size of the alkylating agent and could be either carbon or oxygen.

In the course of our investigations on the sulfenylation of sulfoxides,[5] we became interested in the sulfenylation of β-keto sulfoxides. Preliminary studies[6] were confined to sulfenylation of some methylsulfinyl derivatives by a new procedure namely via PTC using solid K_2CO_3, methane methylthiosulfonate as sulfenylating agent and TEBA in benzene-dichloromethane.

In this communication we wish to report some stereochemical and conformational studies which were developed in connection with the sulfenylation of some β-keto sulfoxides, containing different groups at the sulfur moiety. Table I shows the yields of the mono-sulfenylated products of the keto sulfoxides **1a-e**, employing two methods, in homogeneous phase (I) and by PTC (II).

TABLE I Sulfenylation of β-keto sulfoxides (**1a-e**)

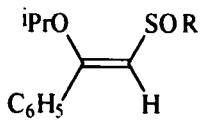
$C_6H_5COCH_2SOR$ ***1***		*$C_6H_5COCH(SMe)SOR$* ***2***			
		Method I[a,b]		*Method II*[c,b]	
	R	*% Yield*	*Diaster. Ratio*	*% Yield*	*Diaster. ratio*
a	Me	84	1:1	57	1:1
b	Et	60	1:1	66	1:1
c	Pr^i	63	1:1	38	1.5:1
d	Bu^t	54	9:1	73	one diaster.
e	C_6H_5	66	1.5:1	28	2:1

a. NaH/DMSO, $MeSO_2SMe$.
b. Isolated yields after column chromatography (hexane:acetone).
c. K_2CO_3, CH_2Cl_2/benzene, $Et_3BnN^+Cl^-$(TEBA), $MeSO_2SMe$.

The α-sulfenylated derivatives **2a-e** contain two asymmetric centers and, therefore, may exist in two diastereomeric forms which can be distinguished on the basis of the ^{1}H NMR spectra. However, while the sulfenylated derivatives **2a** and **2b** show two signals for the methinic proton with ratio 1: 1, **2c** and **2e** exhibit ratios of approximately 1.5:1 and 2:1, respectively, that vary somewhat due to interconversion.[7] However, the t-butyl derivative **2d**, when prepared by method I, exhibited the diastereomeric ratio 9:1 and was shown to be one pure diastereoisomer when prepared by method II.

It seemed obvious that this diastereoselectivity should be due to the fact that the attack of the sulfur electrophile would occur only to one unhindered face of the enolate, which is formed intermediately when the α hydrogen atom of the keto sulfoxide is removed by a base. Therefore, it was presumed that the configuration and conformation of the α-t-butyl sulfinyl enolate should be of importance for the elucidation of the diastereoisomeric excess in the corresponding sulfenylated β-keto sulfoxide.

The proofs for the geometry of the α-sulfinyl enolates were provided by trapping these intermediates as enol ethers. This was possible when the β-keto sulfoxides **1a,d** were submitted to reaction with i-propyl iodide under the same conditions described for the methylsulfinyl derivative.[4] The corresponding i-propyl enol ethers **3a,d** showed in the ^{1}H NMR spectra only one methinic proton. This suggests the presence of only one stereoisomer which, by an ^{1}H NMR NOE difference experiment, was shown to be of the Z configuration.[8].



R = Me (a), ^{t}Bu (d)

3

In the case of the solid t-butyl derivative, the final proof for the Z configuration was obtained from the X-ray analysis[9] (Figure 1). It indicates clearly that S=O and C-O are gauche. It is noteworthy that similar gauche rotamer was proposed recently for the β-keto t-butyl sulfoxide.[10] It may be seen also that only one face of the enolate is unhindered and thus, available to the attack of sulfur electrophile. Therefore, the diastereoselectivity in formation of the sulfenylated product arises from the preferred attack of the sulfur electrophile at one face of the enolate as the other one is shielded by t-butyl group.

TABLE II Physical, ^{1}H NMR and elemental analysis for α-methylsulfanyl β-keto sulfoxides **2b-e** and i-propyl enol ether **3d**

Compd.	*^{1}H NMR* $\delta(CDCl_3)$	*Molecular formula*		*Analysis (%)* *C*	*H*
2b	1.35 and 1.46 (t, J = 11 Hz, t, J = 1Hz, total 3H), and 2.26 (s, s, total 3H), 2.59- 2.72 and 2.91–3.07 (m, m, total 2H), $C_{11}H_{14}O_2S_2$ 5.17 and 5.26 (s, s, total 1H) 7.46–7.69 (m, 3H) and 8.00–8.10 (m, 2H)	$C_{11}H_{14}O_2S_2$	Calc.	54.52	5.82
			Found	54.61	5.92
2c	1.19, 1.34, 1.38 and 1.47 (d, J = 10 Hz, d, J = 10 Hz, d, J = 11 Hz, d, J = 11 Hz,total 6H), 2.14 and 2.24 (s, s, total 3H), 2.98 and 3.45 (m, m, total 1H), 5.03 and 5.14 (s, s, total 1H), 7.45–7.70 (m, 3H), 7.99–8.06 (m, 2H)	$C_{12}H_{16}O_2S_2$	Calc.	56.22	6.29
			Found	55.85	6.36
2d	1.24, (s, 9H), 2.25 (s, 3H), 4.96 (s, 1H), 7.46–7.61 (m, 3H), 7.96–8.00 (m, 2H)	$C_{13}H_{18}O_2S_2$	Calc.	57.74	6.71
			Found	57.48	6.64
2e	1.97 and 2.36 (s, s, 3H), 4.96 and 5.02 (s, s, 1H), 7.25–8.01 (m, 10H)	$C_{15}H_{14}O_2S_2$	Calc.	62.04	4.86
			Found	62.09	4.92
3d	1.24, (d, 3H, J = 6Hz), 1.27 (s, 9H), 1.29 (d, 3H, J = 6 Hz), 4.20 (h, 1H, J = 6Hz), 5.68 (s, 1H), 7.41–7.53 (m, 5H)	Calc. $C_{15}H_{22}O_2S_2$ m.p. 80–82°C	Calc.	67.63	8.32
			Found	67.42	8.04

In conclusion, the sulfenylation reaction of some β-keto sulfoxides, containing different groups at the sulfinyl moiety, by the homogeneous and PTC solid-liquid methods, were described, and proofs were provided for the Z configuration of the intermediate enolates. The stereoselectivity observed in the case of the sulfenylated t-butyl derivative was attributed to the configuration as well as to the conformation of the corresponding enolate.

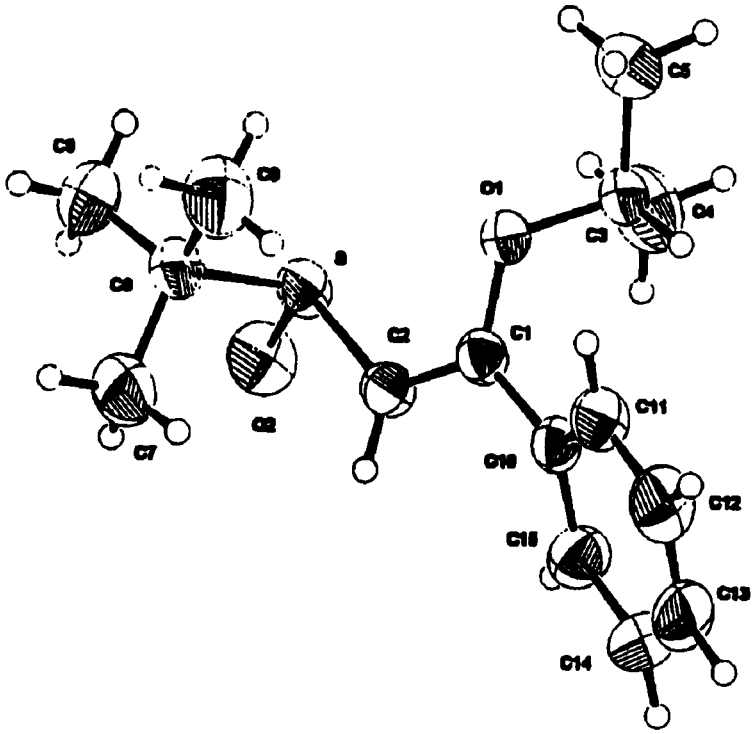


FIGURE 1 X-ray of i-propyl enol ether **3d**

EXPERIMENTAL

Melting points were uncorrected and were determined on a Koffler hot-stage apparatus. ^{1}H NMR spectra were recorded on a Bruker AC-200

spectrometer. NOE difference experiments were performed using the same instrument.

Microanalyses were performed on a Perkin Elmer 2400 CHN elemental analyzer. Column chromatography was done with Merck 60 (70–230 mesh) silica.

β-Keto sulfoxides **1a-e** were prepared according to literature procedures.[10–14]

For General Procedures for the sulfenylation of β-keto sulfoxides in homogeneous medium and under phase transfer condition, see previous paper.[6]

Enol ether **3d** was prepared as previously described for **3a**.[4]

Physical, ^{1}H NMR and elemental analysis data for all new compounds are presented in Table II.

Acknowledgements

We thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Pesquisa (CNPq) for financial support.

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[8] NOE enhancement was observed for aromatic protons signal of i-propyl enol ethers corresponding to **1a,d** by irradiating at the olefinic proton signal frequency and vice-versa.
[9] Crystal data for compound: $C_{15}H_{30}O_2S$, M 274.45. Crystal size 0.20 × 0.15 × 0.10 mm. T = 293K. Crystal system: triclinic, space group P1, a = 8.888 (1)Å, b = 9.733 (1)Å, c = 10.546 (2)Å, α = 89,33 (2)Å, β = 69.84 (1)Å, γ = 65.65 (1)Å, v = 771.1 (2)Å^3, D_c = 1.182 g/cm^3, μ = 0.204 mm^{-1}. R_1 = 0.0457 wR_{all} = 0.1308. Full structural details have been deposited with the Cambridge Crystallographic Data Centre.
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