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SULFENYLATION OF β-KETO SULFOXIDES. III. DIASTEREOSELECTIVITY INDUCED BY A CHIRAL PHASE TRANSFER CATALYST.

Blanka Wladislaw,* Liliana Marzorati,* Francisco C. Biaggio,[a] Reinaldo R. Vargas, Marcelo B. Bjorklund and Julio Zukerman-Schpector.[b]

Instituto de Química, Universidade de São Paulo, Caixa Postal 26.077, CEP. 05599-970, São Paulo - S.P., Brazil

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Abstract: The asymmetric induction in the sulfenylation of several β-keto sulfoxides under phase transfer catalytic conditions in the presence of the chiral catalyst N-benzylquininium chloride was investigated. It is concluded that the diastereoselectivity is not accompanied by enantiomeric resolution.

Key Words: Stereoselection, enolates, sulfinyl compounds, phase transfer, catalysis.

INTRODUCTION

The sulfenylation reactions of sulfoxides and sulfones have been the subject of continuing interest in our laboratory.[1-7] Recent investigations[8,9] showed that PTC procedure in a two-phase solid-liquid system, using solid potassium carbonate as base, TEBA as catalyst and methyl methanethiolsulfonate as sulfenylating agent, in dichloromethane - benzene, is a convenient method for sulfenylation of carboxylic acid derivatives activated by α-sulfinyl or α-sulfonyl groups. This method was also shown to be successful for the sulfenylation of β-keto sulfoxides.[10,11]

In the course of these latter investigations we became interested in verifying whether diastereoselectivity could be induced in the C-S bond formation by employing a chiral catalyst instead of TEBA.

A large number of enantioselective reactions induced by chiral catalysts are described in the literature. Particularly worthy of mention are the excellent results of enantioselective methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone and other α-aryl substituted carbonyl compounds using substituted N-benzylcinchoninium halides as chiral catalysts[12,13] and recent investigations[14-18] on asymmetric alkylations employing chiral catalysts containing a structurally rigidified cinchona alkaloid system and protected hydroxyl groups. However, very few examples of diastereoselective reactions induced by chiral catalysts have been reported, the aldol condensation of α-amino esters with aldehydes to give β-hydroxy amino acids[19,20] being an interesting example of such reaction.

*Corresponding author FAX 55-11-815-5579

[a]On partial leave from Engenharia Química de Lorena, Lorena, S.P. [b]To whom the correpondence on X-ray structure should be addressed.

bwlad@quim.iq.usp.br; marzora@quim.iq.usp.br; biaggio@dequi.faenquil.br; rrvargas@quim.iq.usp.br; malbb@quim.iq.usp.br; julio@power.ufscar.br

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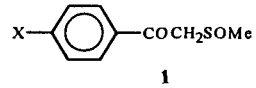
RESULTS AND DISCUSSION

The sulfenylation reactions were performed as previously described[10,11] in a two-phase solid-liquid system, TEBA being substituted by commercially available N-benzylquininium chloride (QUIBEC). The yields of the sulfenylated products **2a,b**, obtained from the β-keto sulfoxides **1a,b** are shown in Table 1. The analysis of the ^1H NMR spectra of the crude reaction products revealed that the diastereomeric ratio in both cases is 4:1.

TABLE 1. PTC sulfenylation* of some N-methylsulfinyl acetophenones **1a,b** using QUIBEC**



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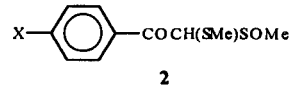

2

		Yield % (isolated)	d.r.
a	X=H	55	4:1
b	X=Me	47	4:1

*Solid K_2CO_3, $MeSO_2SMe$, benzene/CH_2Cl_2; **N-benzylquininium chloride.

However, this diastereomeric excess was only reproducible when all reagents were rigorously anhydrous and when the catalyst was rapidly removed by filtering through a silica column as soon as the reaction was completed. It is noteworthy that the solid sulfenylated product can be kept in the freezer for several weeks without any alteration of the diastereomeric ratio.

The care that must be taken to maintain the diastereomeric excess during the work-up is easily explained by the increased acidity of the α hydrogen of the sulfenylated derivative. It was verified that the presence of the chiral catalyst during the work-up is mainly responsible for the epimerization. The rapid decrease of the diastereomeric excess of the α-sulfenylated β-keto sulfoxide **2a** (16.5:1) in $CDCl_3$ in the presence of QUIBEC is shown in Figure 1. Table 2 indicates that this decrease is much slower in the absence of the catalyst. It seems reasonable to suggest that the enolization promoted by the OH group of the catalyst is responsible for this epimerization.

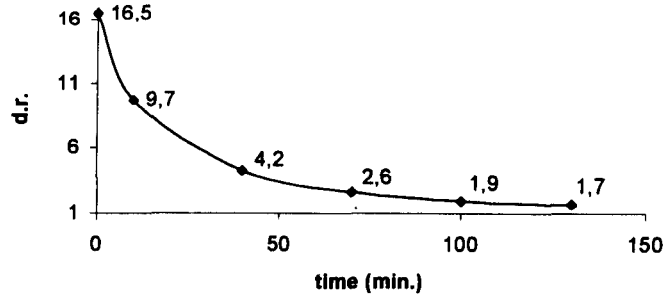

FIGURE 1. Epimerization of the sulfenylated β-keto sulfoxide **2a** in $CDCl_3$ in the presence of QUIBEC 10%.

TABLE 2. Epimerization of the sulfenylated β-keto sulfoxide, **2a**, in $CDCl_3$.

d.r.	Time (h)
16.5 : 1	0
12.5 :1	18
9.0 :1	44

However, it is important to emphasize that, no epimerization occurs during the course of the reaction itself. Thus, the sulfenylated product, isolated after 15 min. of reaction (35% yield), showed the same diastereomeric excess as that after 2 h of reaction.

As for the origin of the observed diastereoselectivity induced by the chiral catalyst, it seems reasonable to suggest that a hydrogen bond between $C\text{-}O^-$ of the enolate and the OH of the chiral catalyst is essential for the formation of a tight ion-pair at the interface.

The necessity of strictly anhydrous conditions for maintaining the reproducibility of the diastereomeric excess suggests that the sulfinylic oxygen, with its well known capacity for hydrogen bonding,[23] participates in a prototropic exchange between OH of the catalyst and $C\text{-}O^-$ of Z enolate.[11,21] As illustrated in Figure 2, formation of the hydrogen bond is possible when either the *Re* or *Si* face of the enolate is blocked by the catalyst with the possibility of π–π interaction between the aromatic ring of enolate and either the N-benzyl ring or the quinoline nucleus of the catalyst. The configurations of the sulfenylated derivatives are shown in Table 3.

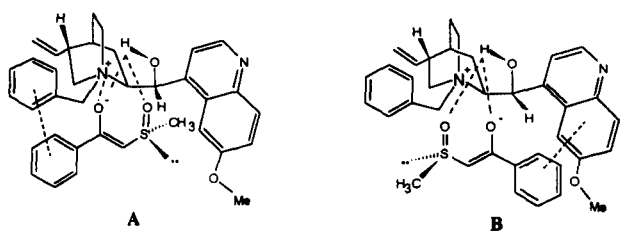

FIGURE 2. QUIBEC - enolate ion – pair for keto-sulfoxide **1a** (S_R). A: interaction with the N-benzyl ring; B: interaction with the quinoline nucleus.

TABLE 3. Stereochemical aspects of the reaction of Z enolates of β-keto sulfoxides with sulfenylating agent in the presence of QUIBEC

Catalyst group that interacts with aromatic ring of enolate	Enolate face blocked by catalyst	Config. of **1a,b**	Config. of **2a,b**
benzyl ring	**Si**	S_R	S_RC_R
	Si	S_S	S_SC_R
quinoline nucleus	**Re**	S_R	S_RC_S
	Re	S_S	S_SC_S

Experimental proof for the occurrence of both interactions and for the configuration of the major sulfenylation product was obtained when optically active β-keto sulfoxide **1a**, of S_R configuration, prepared by chloroperoxidase-catalysed oxidation of the corresponding β-keto sulfide,[22] was submitted to sulfenylation. The optically active sulfenylated derivative obtained, **2a**, exhibited a large diasteromeric ratio of 10:1, most probably due to a double induction. It was crystallized from carbon tetrachloride to give the pure major diastereomer, which by X-ray analysis was shown to have the S_RC_R configuration[24] (Figure 3). Therefore, the minor diastereomer should have the S_RC_S configuration.

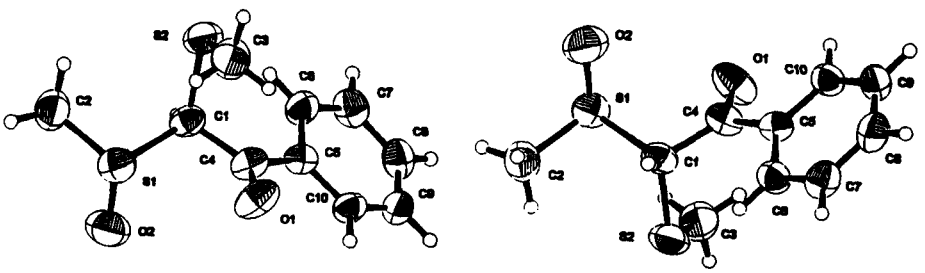

FIGURE 3. X-ray crystallographic structure of the pure major diastereomer of **2a** of S_RC_R configuration.

This result clearly shows that π- π interaction of the aromatic ring of the enolate occurs with the benzyl ring as well as with the quinoline nucleus of the catalyst. However, it was important to verify whether one of these interactions was preferred over the other. If this were the case, both the major and the minor diastereomer obtained from the racemic sulfenylated derivative should show some enantiomeric excess. However, the existence of the enantioselectivity can be rejected because neither the pure major diastereomer (obtained by crystallization of racemic sulfenylated derivative **2a** with an initial diastereomeric ratio of 4: 1) nor the minor diastereomer (obtained by evaporation of the mother-liquor of the latter) showed optical activity.

Therefore, it may be concluded that the diastereoselectivity in the sulfenylation of the racemic keto sulfoxides is not caused by differences in association between enolate and the catalyst. This suggests that it is most probably due to a difference in the rates of attack of the sulfenylating agent on the ion-pair that takes place in the organic phase. In fact, when the sulfinyl enolates of S_R and S_S configuration that give raise to the major RR/SS product are blocked by the catalyst through the *Si and Re* faces, respectively, the lone electron pair of the sulfinyl group is directed to the front, giving free access to the sulfenylating agent. This is contrary to the situation that gives rise to the minor S_SC_R/S_RC_S product, in which the methyl group is directed to the front.

Additional proof for the association between the enolate and chiral catalyst was obtained when β-keto sulfoxides **1c-e** were submitted to sulfenylation under the same conditions as employed previously for **1a-b** (Table 4).

TABLE 4. Sulfenylation of some β-keto sulfoxides in PTC conditions*, employing QUIBEC.

	$RCOCH_2SOR'$ 1	$RCOCH(SMe)SOR'$ 2	
		Yields %**	d.r.
c	R = R' = Me	29	1:1
d	R = Me; R'= Ph	31	1:1
e	R = R' = Ph	46	1.5:1

*Solid K_2CO_3, $MeSO_2SMe$, benzene - CH_2Cl_2; **Isolated.

The absence of a diastereomeric excess in the case of the sulfenylated derivatives **2c,d,** in which there is no phenyl group attached to the carbonyl moiety, clearly shows the importance of π- π interaction for the formation of the tight ion-pair. As for the compound **1e**, in which two phenyl groups are present, several factors may contribute to the absence of diastereoselectivity, such as difficulties in formation of an ion-pair reflecting the decreased basicity of the sulfinyl oxygen[23] or steric hindrance to approximation of the catalyst or the lack of a difference in the rates of attack of sulfenylating agent on the blocked enolates. However, the fact that the diastereomeric ratio (1.5:1) is the same as that in the presence of TEBA[11] suggests that lack of formation of an ion-pair is responsible for the absence of diastereoselectivity.

It should be mentioned that sulfenylation of the chiral β-keto sulfoxide **1a,** under PTC conditions using a chiral catalyst, is of interest as a convenient alternative method for the synthesis of protected enantiopure α-hydroxy aldehydes,[25,26] which may be of R or S configuration, depending on the configuration of the chiral catalyst.

Further investigations using third generation catalysts with protected OH group[18] may provide new insight into the mechanism for this diastereoselective reaction.

In summary, it is shown that diastereoselective sulfenylation of β-keto sulfoxides can be achieved under PTC conditions using QUIBEC as chiral catalyst. Proof is provided for the configuration of the major sulfenylated products and for the absence of enantioselectivity. The dual role of the chiral catalyst - promotion of diastereoselectivity and epimerization - is discussed. The potential for application to the synthesis of enantiopure substituted aldehydes is pointed out.

EXPERIMENTAL SECTION

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer in $CDCl_3$, using Me_4Si as internal standard. Elemental analyses were performed on a Perkin Elmer 240B elemental analyzer. Optical rotation measurements were performed using a JASCO DIP 370 polarimeter at λ = 589 nm and column chromatography was done with Merck 60 (70-230 mesh) silica. β-Keto sulfoxides **1a,b,e** were prepared according to literature procedures.[10,27] β-Keto sulfoxides **1c,d**[28] were prepared from haloacetone by reaction with sodium thiolate,[29] followed by oxidation with hydrogen peroxide.[30]

General procedure for sulfenylation of β-keto sulfoxides (**1a-e**) under phase-transfer conditions using QUIBEC as catalyst:

To a mixture of β-keto sulfoxide **1** (2.1 mmol), and N-benzylquininium chloride (0.094 g, 0.21 mmol) dissolved in benzene/dichloromethane (1:1, total volume 4.0 mL), anhydrous potassium carbonate (2.2 mmol) was added in one portion. Methyl methanethiolsulfonate (2.2 mmol) was added at r.t., to the vigourously stirred two phase system and the mixture was stirred for 2 h. After addition of 30 mL of dichloromethane and filtration, the organic extract was dried over anhydrous $MgSO_4$ and concentrated under vaccum. The crude product was subjected to column chromatography (hexane/acetone 8:2 v/v) to give monosulfenylated product **2**.

ω-(Methylthio)- ω -(methylsufinyl)acetophenone (2a).[10] Yield 55%. ^{1}H NMR chemical shifts for diastereoisomers were in agreement with previously reported ones;[31] the diastereoisomeric ratio was 1:4. When optically active **1a**[22] was employed as starting material, the yield was 45% and the isomeric ratio 1:10; $[\alpha]^{20}$ +20.5(c=2.0, $CHCl_3$). The major diastereoisomer was isolated upon crystallization using carbon tetrachloride as solvent. ^{1}H NMR ($CDCl_3$) δ 2.20 (s,3H), 2.89 (s,3H), 5.25 (s,1H), 7.49-7.64 (m, 3H); 8.05-8.07 (m,2H), $[\alpha]^{20}$+22.5(c=0.8, $CHCl_3$).

ω-(Methylthio)- ω-(methylsulfinyl)-p-methylacetophenone (2b).[10] Yield 47%. Diastereoisomeric ratio 1:4. ^{1}H NMR δ 2.15 and 2.23 (ds,3H), 2.42 (s,3H), 2.65 and 2.86 (ds,3H), 5.28 and 5.37 (ds, 3H), 7.30 (d,2H), 7.94 (d,2H).

α-(Methylthio)-α-(methylsulfinyl)acetone (**2c**). Yield 29%. Diastereoisomeric ratio 1:1. ^{1}H NMR δ 2.18 and 2.24 (ds,3H), 2.44 and 2.45 (ds,3H), 2.64 and 2.79 (ds,3H), 4.37 and 4.53 (ds, 1H). Calcd. for $C_5H_{10}O_2S_2$: C, 36.14; H, 6.02. Found: C, 36.05; H, 6.04.

α-(Methylthio)- α-(phenylsulfinyl)acetone (2d). Yield 31%. Diastereoisomeric ratio 1:1. ^{1}H NMR δ 1.94 and 2.13 (ds,3H), 2.27 and 2.39 (ds,3H), 5.01 and 5.12 (ds,1H), 7.51-7.83 (m, 5H). Calcd. for $C_{10}H_{12}O_2S_2$: C, 52.61; H, 5.30. Found: C, 53.01; H, 5.27.

ω-(Methylthio)-ω -(phenylsulfinyl)acetophenone (2e).[11] Yield 46%. Diastereoisomeric ratio 1:1.5. ^{1}H NMR δ 1.97 and 2.36 (ds,3H), 4.96 and 5.02 (ds, 1H), 7.25-8.01 (m, 5H).

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