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Phase Transfer Catalysis (PTC) Sulfanylation of Some 2-Methylsulfinyl-Cyclanones

Blanka Wladislaw,* Mauro Alves Bueno, Liliana Marzorati, Claudio Di Vitta, and Júlio Zukerman-Schpector[†]

Instituto de Química, Universidade de São Paulo, CEP 05599-970, São Paulo, S.P., Brazil, and Centro de Ciências Exatas e de Tecnologia, Universidade Federal de São Carlos, São Carlos, S.P., Brazil

bwlad@iq.usp.br

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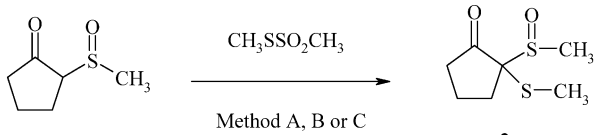
Abstract: The sulfanylation reactions of 2-methylsulfinylated cyclopentanone, 1-indanone, and cyclohexanone by a PTC procedure are reported and the yields and diastereoselectivity compared to those obtained by the homogeneous-phase method. The stability of the sulfanylated methylsulfinyl derivatives at room temperature versus the instability of the *p*-tolylsulfinyl derivatives is also reported.

Previous reports from this laboratory[1−3] showed that a solid−liquid PTC procedure is a convenient method for sulfanylation of some sulfinyl acetophenones, esters, and thiolesters, as well as α-sulfonyl esters and thiolesters. This communication reports the sulfanylation of some racemic 2-sulfinyl cyclanones by the same procedure. Thus, when 2-methylsulfinylcyclopentanone (**1**) was submitted to sulfanylation using K_2CO_3 as the base, *S*-methylmethanethiolsulfonate as the sulfanylating agent, and benzyltriethylammonium chloride (TEBA) as the catalyst in CH_2Cl_2/benzene at room temperature, the sulfanylated product **2** was obtained in 80% yield (Scheme 1, method A). However, the sulfanylated derivative **2** was obtained in low yield (39%) employing K_2CO_3 as the base and the same sulfanylating agent, but in the absence of TEBA (Scheme 1, method B). It should be mentioned that the sulfanylation of **1** by a homogeneous-phase method also proved to be successful, giving the sulfanylated product **2** in 84% yield (Scheme 1, method C).

Although the sulfanylation of **1** could give rise to two diastereoisomers, only one was obtained, independent of the method employed. This high diastereoselectivity (100%) is undoubtedly due to the fact that the attack of the sulfur electrophile occurs only at the unhindered face of the enolate, which is formed when the α-hydrogen atom of **1** is removed by base.

The solid **2** was shown to have the 2*S**S*S** relative configuration by X-ray analysis (Figure 1).

SCHEME 1. Sulfanylation Reaction of 2-Methylsulfinylcyclopentanone (1)



1 **2**

Method A: K_2CO_3, TEBA, CH_2Cl_2, Benzene, rt; (80%); B: K_2CO_3, CH_2Cl_2, Benzene, rt; (39%); C: LDA, THF, -78° C (84%).

This indicates that only the *Re* face of the (S)*S** enolate and the *Si* face of the (S)*R** enolate is attacked by the sulfanylating agent, most probably due to the steric hindrance. This can be rationalized by assuming that, in the enolate, the C−O and S−O bonds are in a syn periplanar orientation, due to interaction of the oxygen atoms with the ammoniun cation.[4] Thus, the CH_3 group would prevent attack at the face on which it is located (Figure 2). It should be mentioned that this is the first time that the facial diastereoselectivity of the sulfanylation reaction of such sulfinyl cyclanones enolates could be determined.[5]

These results led us to investigate the sulfanylation reaction of the 2-*p*-tolylsulfinylcyclopentanone (**3**). It has been reported that 2-*p*-tolylsulfinylcyclohexanone undergoes sulfanylation by the homogeneous-phase method, at low temperature, but that the corresponding sulfanylated product is unstable at room temperature and, therefore, could not be isolated and characterized.[5] In fact, when **3** was submitted to sulfanylation under PTC conditions, instead of the sulfanylated derivative **4**, the elimination product, 2-methylsulfanylcyclopenten-2-one (**5**), was obtained (Scheme 2).

The difference in behavior between cyclic methylsulfinyl and *p*-tolylsulfinyl ketones may be attributed to the difference in leaving group character between *p*-tolyl and methylsulfinyl groups.

We then investigated the sulfanylation of 2-methylsulfinyl-1-indanone (**6**), in which the condensed benzene ring should increase the planarity of the intermediate enolate. When **6** was submitted to sulfanylation in the absence of TEBA, no sulfanylated product was obtained. However, under PTC conditions, the sulfanylated derivative **7** was obtained in 85% yield (Scheme 3, method A).

In addition, the sulfanylated derivative **7** was obtained in only a 70% diastereomeric excess (de) as compared to the cyclopentanone derivative **2**, which was formed as a single diastereoisomer.

The sulfanylation of 2-methylsulfinylcyclohexanone (**8**) by the PTC procedure was successful and gave the amorphous solid sulfanylated derivative **9** in 75% yield (Scheme 4, method A). It should be mentioned that the homogeneous-phase method afforded only a 47% yield

[†] Universidade Federal de São Carlos.

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(4) Alvarez-Ibarra, C.; Csáky, A. G.; Maroto, M.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 6700−6705.

(5) In a study of the sulfanylation of 2-*p*-tolylsulfinylcyclohexanone, the sulfanylated derivatives proved to be unstable, precluding assignment of their relative configurations. See: Ruano, J. L. G.; Barros, D.; Maestro, M. C.; Alcudia, A.; Fernandes, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3445−3453.

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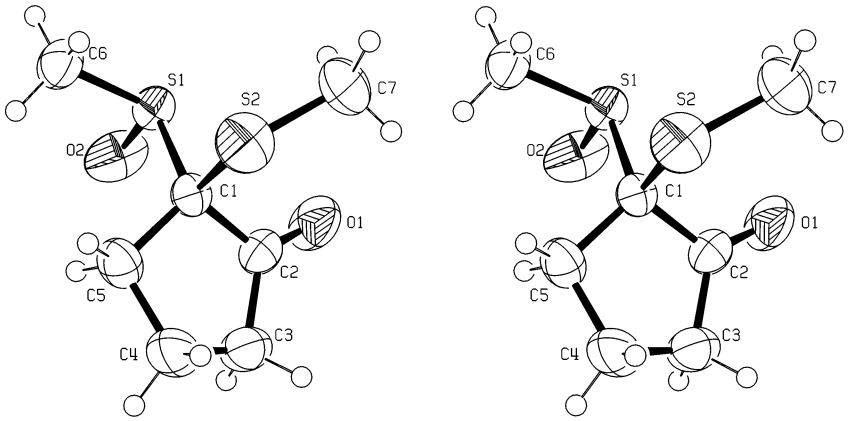


FIGURE 1. ZORTEP drawing of **2** in stereoview.

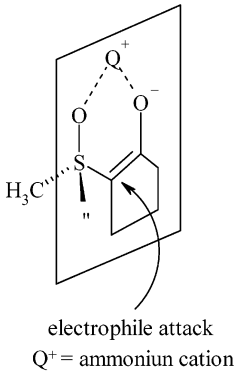


FIGURE 2. Preferred conformation for the chelated enolate of **1**.

(Scheme 4, method C) of the sulfanylated product **9**. It is noteworthy that, while the sulfanylated product **9** obtained by the PTC procedure (Scheme 4, method A) exhibited a de of only 20%, the de of the product from the homogeneous method (Scheme 4, method C) was 50%. The higher diastereoselectivity in the latter case is presumably due to the lower temperature employed (−70 °C). However, the determination of the stereochemical course of this sulfanylation reaction was only possible by preparing the crystalline sulfanylated derivative **10** (Scheme 4), whose major diastereoisomer was submitted to X-ray analysis.

The major diastereoisomer of **10** was shown to have the 2*S**S*S** configuration (Figure 3) and, therefore, the same as that of the sulfanylated cyclopentanone derivative **2**.

Table 1 shows the yields and de values for the sulfanylation of some 2-sulfinyl cyclanones, in comparison to some open-chain ketosulfoxides, previously sulfanylated in our laboratory by the PTC method.[3]

TABLE 1. Yields and de Values for the PTC Sulfanylation[a] Reactions of Some Sulfinyl Ketones

compound	product	yield (%)	de (%)
1	**2**	80	100
6	**7**	85	70
8	**9**	75	20
8	**10**[b]	93	40
$PhCOCH_2SOCH_3$[c]	$PhCOCH(SCH_3)SOCH_3$	57	0
$PhCOCH_2SOCH(CH_3)_2$[c]	$PhCOCH(SCH_3)SOCH(CH_3)_2$	38	15
$PhCOCH_2SOC(CH_3)_3$[c]	$PhCOCH(SCH_3)SOC(CH_3)_3$	73	100

[a] Using $CH_3SSO_2CH_3$; [b] Using *p*-$TolSSO_2CH_3$; [c] See ref 3.

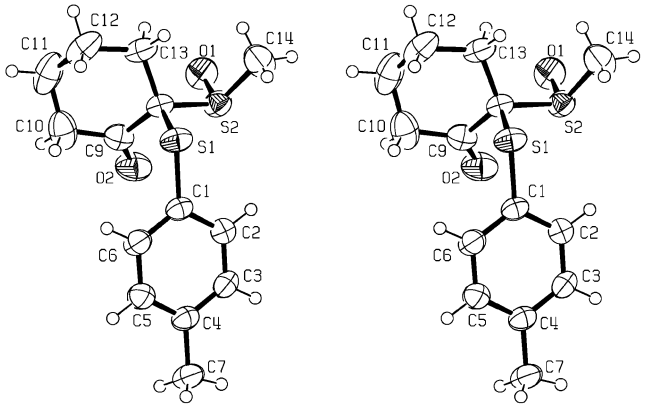
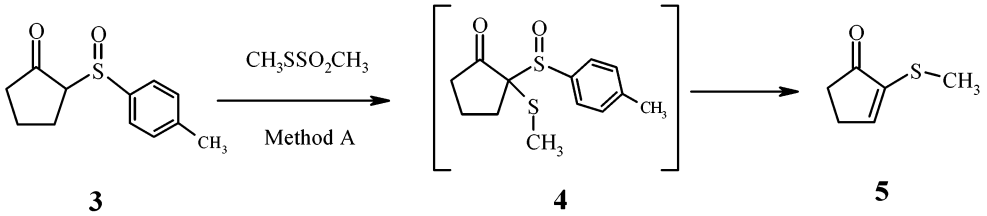


FIGURE 3. ORTEP drawing of the major diastereoisomer of **10** in stereoview.

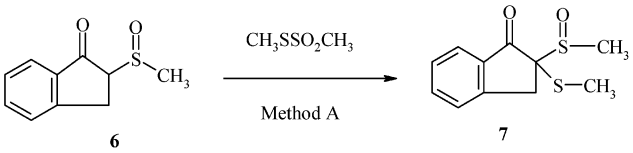
The 100% de value for **2** is the same as that for the open-chain *tert*-butyl derivative, being, in both cases, of steric origin. Further studies on the sulfanylation of enantiomerically pure 2-methylsulfinyl cyclanones will be reported in due course.

In summary, it has been shown that the PTC procedure is a convenient method for obtaining sulfanylated 2-

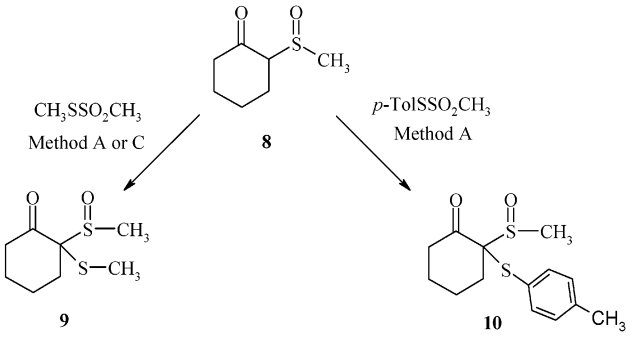
SCHEME 2. Sulfanylation Reaction of 2-*p*-Tolylsulfinylcyclopentanone (3)



SCHEME 3. Sulfanylation Reaction of 2-Methylsulfinyl-1-indanone (6)



SCHEME 4. Sulfanylation of 2-Methylsulfinylcyclohexanone (8)



methylsulfinyl cyclanones in good yields and, in some cases, in high de. A rationalization for the observed facial diastereoselectivity of the performed sulfanylation reaction is proposed.

Experimental Section

General Procedures for the Sulfanylation of 2-Methylsulfinyl Cyclanones: Method A (PTC). A mixture of the 2-methylsulfinyl cyclanone (0.50 mmol), $CH_3SSO_2CH_3$ or *p*-$TolSSO_2CH_3$ (0.50 mmol), solid K_2CO_3 (1.0 mmol), and TEBA (0.10 mmol) in 5 mL of benzene/dichloromethane (1:1, v/v) was vigorously stirred at room-temperature. The reaction progress was monitored by TLC, and after reaching equilibrium, the mixture was diluted with dichloromethane and the solid removed by vacuum filtration. After concentration of the filtrate, the crude product was purified by chromatography (TLC; *n*-hexane/ethyl acetate, 3:2, v/v).

Method C (Homogeneous-Phase). *n*-Butyllithium (0.58 mL of a 2 M solution in hexanes, 1.2 mmol) was added dropwise to a cooled solution (0 °C) of diisopropylamine (0.16 mL, 1.2 mmol) in 10 mL of THF. After 10 min of stirring, the solution was cooled to −78 °C, and the 2-methylsulfinyl cyclanone (1.1 mmol) dissolved in 3 mL of THF was added via syringe. Stirring was maintained for 30 min at the same temperature, and $CH_3SSO_2CH_3$ (1.1 mmol) in THF (5 mL) was added. After 5 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with chloroform (3 × 15 mL). The organic extract was dried ($MgSO_4$), the solvent removed under vacuum, and the crude product purified by TLC (*n*-hexane/ethyl acetate, 3:2, v/v).

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Supporting Information Available: Characterization data for compounds **1**−**3** and **5**−**10** and ^1H and ^{13}C NMR spectra of compounds **2**, **6**, **7**, **9**, and **10** (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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