Novel Uncatalyzed Thermal Pummerer Rearrangements

B. Wladislaw,* L. Marzorati, and F. C. Biaggio

Instituto de Química, Universidade de São Paulo, CP 20.780, CEP. 01498-970, Sao Paulo, S.P., Brazil

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The sulfenylation reaction of benzylic sulfones has been shown to be a useful method of obtaining the corresponding α-methylthio sulfones, which, in analogy to α-methylthio sulfoxides,[1] were shown to be precursors, through thermal decomposition of the corresponding carbonyl compounds.[2-6]

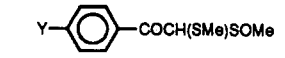
We were interested in extending this method to the sulfenylation of β-keto sulfoxides, which may be easily obtained by condensation of carboxylic esters with dimsyl anion,[7] and in investigating the thermal decomposition of the α-sulfenylated β-keto sulfoxides. This would be an alternative method for preparation of these compounds, as the reported one[8] involves condensation of carboxylic esters with methyl (methylthio)methyl sulfoxide.

Two procedures, both using *S*-methyl methanethiosulfonate as the sulfenylating agent, were employed for sulfenylation of the β-keto sulfoxides **1a–d**. The first (procedure A) was in homogeneous medium, using NaH as base in DMSO; the second (procedure B) employed a two-phase catalytic procedure, using K_2CO_3, benzene/dichloromethane, and TEBA. The results (Table I) show that the yields of the α-methylthio-substituted β-keto sulfoxides **2a–d** are slightly higher by procedure A. However, the simplicity of procedure B makes it more attractive. Compounds **2a–d**, obtained by both procedures, were shown to be mixtures of two diastereoisomers in equal proportions.

The α-methylthio β-keto sulfoxides **2a–d** underwent decomposition when heated at 75 °C for 2 h in the absence of a solvent. However, instead of the expected α-keto aldehydes **3a–d**, which would result from the sulfoxide–sulfenate rearrangement,[9,10] mixtures of the corresponding α-keto thioesters **4a–d** and α-keto ortho trithio esters **5a–d** were obtained in equal proportions (Scheme I).

The fact that the same mixture **4a** and **5a** was obtained when **2a** was submitted to the acid-catalyzed Pummerer rearrangement, by treatment with aqueous hydrochloric acid, indicates that in the thermal decomposition an uncatalyzed Pummerer rearrangement takes place. It seems reasonable to suggest that such a rearrangement would be initiated by an acidic proton transfer from the α-carbon to the sulfinyl group. Both products, **4** and **5**, could originate from a common intermediate **6**, which would lose methanethiol slowly to yield the α-keto thioester **4**, but the unchanged **6** would react with methanethiol to give the α-keto ortho trithio ester **5** (Scheme II).

Table I. Sulfenylation of β-Keto Sulfoxides 1a–d Using $MeSO_2SMe$



sulfenylation products	Y	yields (%)[a] A[b]	B[c]
2a	H	84	67
2b	*p*-Cl	90	45
2c	*p*-Me	58	45
2d	*p*-MeO	45	65

[a] Isolated products. [b] NaH/DMSO. [c] K_2CO_3/benzene, dichloromethane, $[Et_3NBn]^+Cl^-$ (TEBA).

Evidence for this proposal was obtained when the thermal decomposition of **2a** was performed under a positive pressure of oxygen, and α-keto thioester **4a** was isolated in nearly quantitative yield. It is noteworthy that the mixture of **4** and **5** was transformed totally into **4** by treatment with $I_2/NaHCO_3$.[11]

It became of interest to find out if the thermal decomposition would also occur in the case of the non-sulfenylated β-keto sulfoxides **1**, in which the methylene hydrogens could be still sufficiently acidic to act as proton donors. In fact, we found that the decomposition of **1a,b** occurred at 85 °C to give two main products, α-keto thioesters **4a,b** and ω-methylthioacetophenones **7a,b**, in approximately equal proportions. However, the catalyzed Pummerer rearrangement of the β-keto sulfoxide **1** was reported[12] to give the hemimercaptal of phenylglyoxal **8** as the only reaction product (Scheme III).

A plausible explanation, which can be given for this different result of the thermal decomposition reaction is that the formation of the hemimercaptal of phenylglyoxal **8** also occurs, but to a lesser extent, as compared to the Pummerer-catalyzed reaction. Therefore, the hemimercaptal **8** could undergo oxidation by the unreacted β-keto sulfoxide **1** to give keto thioester **4** and ω-methylthioacetophenone **7** (Scheme III). Such oxidation by the sulfinyl group of the β-keto sulfoxide in the absence of an external electrophile[13] is unusual and could be explained by the presence of acidic methylene hydrogens responsible for protonation of the sulfinyl oxygen, and by stabilization of the resulting oxosulfonium intermediate by hydrogen bonding. The possibility of disproportionation of **8** to **4** and **7** was eliminated since **8**, upon heating to 85 °C, was recovered unchanged.

In summary, we have found that sulfenylation of the β-keto sulfoxides by the phase-transfer catalytic procedure is a convenient alternative method for preparation of the α-methylthio β-keto sulfoxides. The latter compounds undergo uncatalyzed Pummerer rearrangement, which is identical to that which occurs by acid catalysis in aqueous medium. However, the products obtained by thermal decomposition of the unsubstituted β-keto sulfoxides are different from those resulting from the acid-catalyzed Pummerer rearrangement. An uncatalyzed Pummerer

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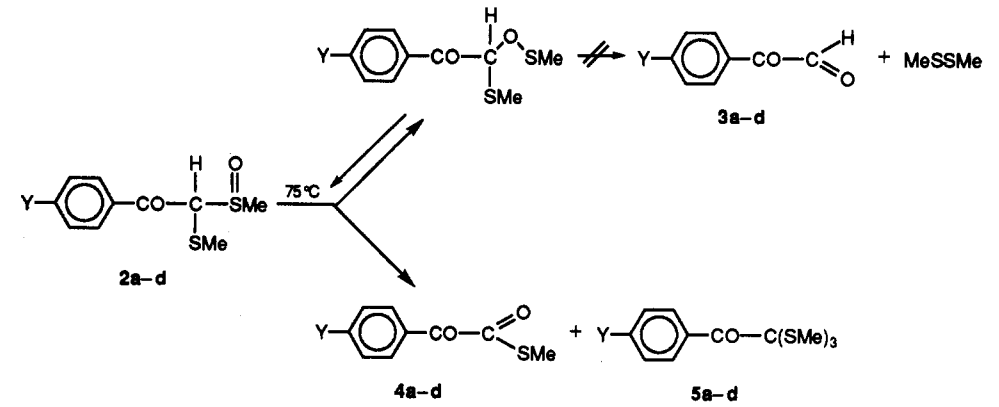
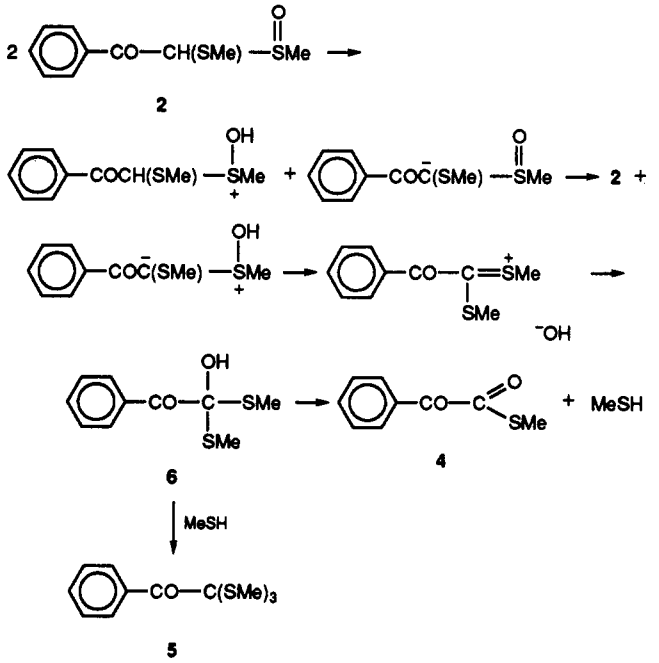
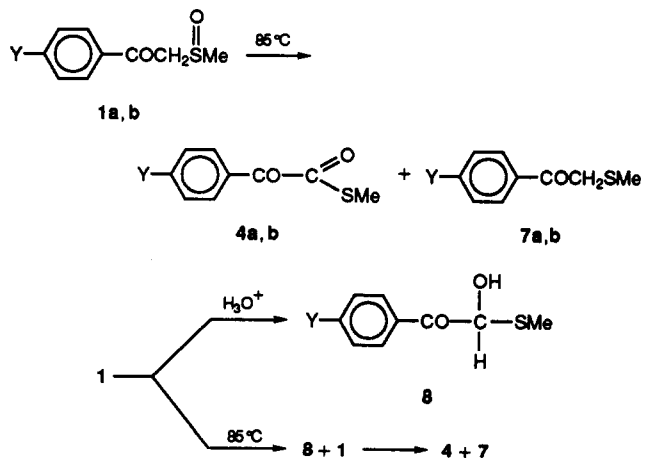
Scheme I



Scheme II



Scheme III



reaction, followed by an oxidation–reduction process, is proposed to be responsible for the observed results.

Experimental Section

Melting points are uncorrected and were determined on a Koffler hot-stage apparatus. IR spectra were recorded on a Perkin-Elmer 238A Fourier-transform instrument. ^{1}H NMR spectra were recorded on a Varian T-60 or a Brüker AC-200 spectrometer, using Me_4Si as internal standard. Microanalyses were performed in our department on a Perkin-Elmer 240B elemental analyzer. GC analyses were performed with a Hewlett-Packard gas chromatograph equipped with a flame ionization detector, a Hewlett-Packard 3392A integrator, and a HP-1 (10 m × 0.53 mm × 2.65 μm film thickness) capillary column. Column chromatography was done with Merck 60 (70–230 mesh) silica. β-Keto sulfoxides **1a–d** were prepared according to literature procedures.[7]

General Procedure for Sulfenylation of β-Keto Sulfoxides 1. A. In Homogeneous Medium. To a suspension of NaH (5.5 mmol, 80% in mineral oil, previously washed with dry hexane) in 5 mL of dry DMSO, under nitrogen at rt, was added a solution of β-keto sulfoxide 1 (2.7 mmol) in 5 mL of dry DMSO, and after stirring for 45 min, *S*-methyl methanethiosulfonate (2.7 mmol), dissolved in 5 mL of dry DMSO, was added. The mixture was further stirred at rt for 2 h and then poured into a saturated NH_4Cl solution. After extraction with CH_2Cl_2, the organic extract was washed with saturated NaCl solution and with water, dried over $MgSO_4$, and concentrated. The crude product was subjected to column chromatography on silica gel, using hexane/acetone (8:2 v/v) as eluent.

B. Under Phase-Transfer Conditions. A mixture of β-keto sulfoxide 1 (2.0 mmol), TEBA (0.20 mmol), K_2CO_3 (4.0 mmol), methyl methanethiolsulfonate (2.0 mmol), benzene (5 mL), and dichloromethane (5 mL) was vigourously stirred for 2 h at rt. After addition of 30 mL of dichloromethane and filtration, the filtrate was concentrated and the residue subjected to column chromatography on silica gel, using hexane/acetone (8:2 v/v) as eluent.

ω-(Methylthio)-ω-(methylsulfinyl)acetophenone (2a). ^{1}H NMR chemical shifts for diastereoisomers were in agreement with previously reported ones,[8] but isomeric ratio was 1:1.

ω-(Methylthio)-ω-(methylsulfinyl)-*p*-chloroacetophenone (2b): ^{1}H NMR ($CDCl_3$) (isomeric ratio 1:1) δ 2.13 and 2.23 (s, s, total 3H), 2.66 and 2.89 (s, s, total 3H), 5.42 and 5.43 (s, s, total 1H), 7.45 (d, 2H), 8.00 (d, 2H). Anal. Calcd for $C_{10}H_{11}O_2S_2$: C, 45.71; H, 4.22. Found: C, 45.84; H, 4.22.

ω-(Methylthio)-ω-(methylsulfinyl)-*p*-methylacetophenone (2c): ^{1}H NMR ($CDCl_3$) (isomeric ratio 1:1) δ 2.14 and 2.23 (s, s, total 3H), 2.42 (s, 3H), 2.64 and 2.86 (s, s, total 3H), 5.31 and 5.40 (s, s, total 1H), 7.94 (d, 2H). Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.52; H, 5.82. Found: C, 54.46; H, 5.69.

ω-(Methylthio)-ω-(methylsulfinyl)-*p*-methoxyacetophenone (2d): ^{1}H NMR ($CDCl_3$) (isomeric ratio 1:1) δ 2.05 and 2.14 (s, s, total 3H), 2.56 and 2.78 (s, s, total 3H), 3.77 (s, 3H), 5.25 and 5.34 (s, s, total 1H), 6.94–7.00 (m, 2H), 7.99–8.08 (m, 2H). Anal. Calcd for $C_{11}H_{14}O_3S_2$: C, 51.14; H, 5.46. Found: C, 51.31; H, 5.79.

Thermal Decomposition of ω-(Methylthio)-ω-(methylsulfinyl)acetophenones 2a–d. Typical Procedure. Compound **2a** was heated, in the absence of solvent, for 2 h at 75–80 °C. GC analysis of crude product showed two main components (approximately 90%), which failed to be separated by column chromatography on silica gel. The identification of these reaction products was carried out by comparison of ^{1}H NMR spectra and

gas chromatography retention times of authentic samples of **4a** and **5a** obtained by independent synthesis.[11] The crude product was treated with $I_2/NaHCO_3$,[11] yielding **4a**, which was isolated in 80% yield.

β-Keto sulfoxides **2b–d** were heated as described above, and authentic samples of **4b–d** and **5b–d** were prepared following the same procedures[11] described for **4a** and **5a**.

ω,ω,ω-Tris(methylthio)-*p*-chloroacetophenone (5b): ^1H NMR ($CDCl_3$) δ 2.00 (s, 9H), 7.10–7.50 (m, 2H), 8.20–8.60 (m, 2H). Anal. Calcd for $C_{11}H_{13}ClOS_3$: C, 45.11; H, 4.47. Found: C, 45.23; H, 4.42.

ω,ω,ω-Tris(methylthio)-*p*-methylacetophenone (5c): ^1H NMR ($CDCl_3$) δ 2.10 (s, 9H), 2.45 (s, 3H), 7.10–7.40 (m, 2H), 8.25–8.55 (m, 2H). Anal. Calcd for $C_{12}H_{16}OS_3$: C, 52.90; H, 5.92. Found: C, 52.97; H, 5.98.

ω,ω,ω-Tris(methylthio)-*p*-methoxyacetophenone (5d): ^1H NMR ($CDCl_3$) δ 2.00 (s, 9H), 3.90 (m, 3H), 6.70–6.95 (m, 4H). Anal. Calcd for $C_{12}H_{16}O_2S_3$: C, 49.97; H, 5.59. Found: C, 50.21; H, 5.73.

***S*-Methyl-(*p*-chlorophenyl)thioglyoxylate (4b):** ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 7.30–7.60 (m, 2H), 8.00–8.30 (m, 2H). Anal. Calcd for $C_9H_7ClO_2S$: C, 50.35; H, 3.28. Found: C, 50.07; H, 3.22.

***S*-Methyl-(*p*-methylphenyl)thioglyoxylate (4c):** ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.45 (s, 3H), 7.00–7.40 (m, 2H), 7.80–8.20 (m, 2H). Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 62.21; H, 5.43.

***S*-Methyl-(*p*-methoxyphenyl)thioglyoxylate (4d).** ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.90 (s, 3H), 6.75–7.05 (m, 2H), 7.95–8.25 (m, 2H). Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79. Found: C, 57.11; H, 4.79.

Thermal Decomposition of ω-(Methylsulfinyl)acetophenones 1a–d. Typical Procedure. Heating of compound **1a** at 80–85 °C, in the absence of solvent, for 2 h yielded two main products which could not be separated by column chromatography on silica gel and were identified by comparison of ^1H NMR spectra and gas chromatography retention times of authentic samples of **4a** and **7a** prepared by independent synthesis.[11,14]

The above procedure was applied to compound **1b**. An authentic sample of **7b**, required for product identification, was synthesized in analogy to **7a**.

ω-(Methylthio)-*p*-chloroacetophenone (7b): ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.60 (s, 2H), 7.15 (d, 2H), 7.99 (d, 2H). Anal. Calcd for C_9H_9ClOS: C, 53.87; H, 4.52. Found: C, 54.22; H, 4.39.

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