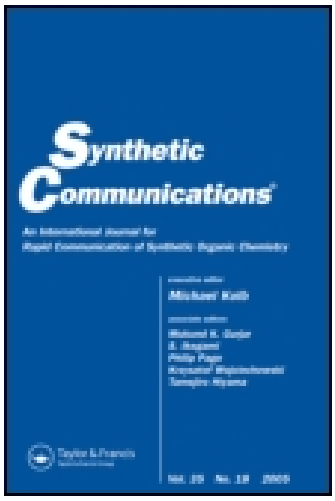

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Chemical Oxidation Studies of β-Hydroxy-sulfides with *tris*(4-Bromophenyl)aminium Hexachloroantimonate: Diastereoselective Sulfoxide Obtaining and Pinacol-Type Rearrangement

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ABSTRACT

The chemical oxidation of some β-hydroxy-sulfides in the presence of *tris*(4-bromo-phenyl)aminium hexachloroantimonate (TBPA) is reported. The oxidation of 2-ethylsulfanyl-cyclohexan-l-ol (*cis*- and *trans*-) resulted the corresponding sulfoxides with good diastereoselectivity (d.e. ≈50%) and for 2-methyl-2-ethylsulfanyl-cyclohexan-l-ol

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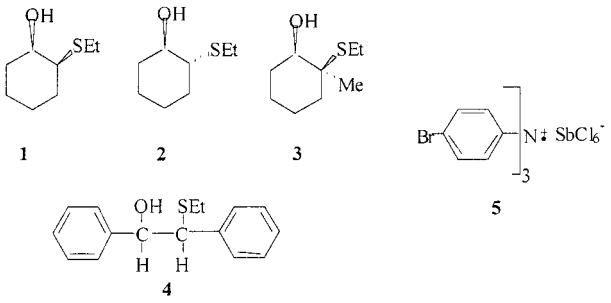
and 2-ethylsulfanyl-1,2-diphenyl-ethanol, the corresponding non-sulfanylated ketones (61–75%) and ethyl ethanethiolsulfonate (51–65%) were obtained via oxidative cleavage and pinacol-type rearrangement.

The β-keto-sulfides and their derivatives are very useful and versatile "synthons" due to the regioselectivity and stereoselectivity they can present.[1] Much more attention has recently been paid to the application of chiral β-keto- and β-hydroxy-sulfoxides in asymmetric synthesis.[2] These useful β-keto-sulfides derivatives with different oxidation states can be achieved through chemical methods.[2] Despite of the increasing interest on organic electrosynthesis, as an useful tool for organic transformations, few works have been reported on the direct electrochemical oxidation[3,4] or reduction[5] studies of β-keto-[3] and β-hydroxy sulfides.[4,5] Even fewer indirect electrochemical studies, through electrogenerated oxidants, with β-hydroxy sulfides have been related. α-phenyl-β-hydroxy-sulfides, for instance, suffer eletrooxidation in the presence of chloride ions (electrogenerated chloronium ion "in situ") resulting in a novel pinacol-type rearrangement to give the corresponding 2-phenyl substituted ketones.[6] α,α-bisphenylthio-β-phenyl-β-hydroxy compounds when indirectly oxidized (with *tris*(4-bromo-phenyl)aminium electrogenerated "in situ") lead to the corresponding ketones with phenyl rearrangement[7]; in similar conditions α-phenylthio-ketones generated the corresponding α-hydroxy-ketone.[7] In a previous work, we reported that β-hydroxy sulfides through indirect anodic oxidation (*tris*(4-bromo-phenyl)aminium electrogenerated "in situ") yielded the corresponding sulfoxides with good diastereoselectivity (d.e. ≅50%).[8]

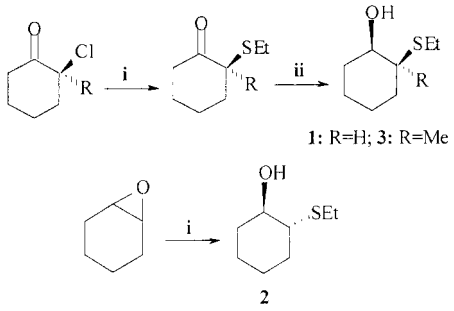
However, the *tris*(4-bromophenyl)aminium can be chemically prepared by some usual methods showing interesting reactivity as oxidant agent[9] and as Diels-Alder catalyst.[10] For example, the chemical oxidation of some ketones, with *tris*(4-bromophenyl)aminium hexachloroantimonate, to their corresponding α-hydroxy derivatives is related.[11] Nevertheless, no chemical oxidation investigation with β-hydroxy sulfides using the *tris*(4-bromophenyl)aminium hexachloroantimonate, commercially available (Aldrich®) has been made yet. As part of this research, we now describe the chemical oxidation study of some β-hydroxy sulfides such as: *cis*- (**1**) and *trans*-2-ethylsulfanyl-cyclohexan-1-ol (**2**), *cis*-2-methyl-2-ethylsulfanyl-cyclohexan-1-ol (**3**), and 2-ethylsulfanyl-1,2-diphenyl-ethanol (**4**) with *tris*(4-bromophenyl)aminium hexachloroantimmonate, TBPA (**5**).



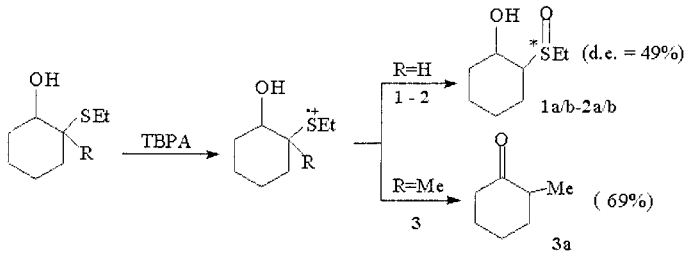
The desired β-hydroxy-sulfides **1–4** and TBPA were prepared in good yields by classical methods[12–15] (Sch. 1).

The chemical oxidation of *cis*- (**1**) and *trans*-2-ethylsulfanyl-cyclohexanol (**2**) with TBPA, and sodium carbonate (1:2:4 mol/mol) in acetonitrile/water (9:1 v/v) yielded (63–69%) the corresponding diastereomeric sulfoxides (**1a** and **1b**, **2a** and **2b**) in good diastereoselectivity (ca. 75:25%) (Sch. 2a). The same condition of 2-methyl-2-ethylsulfanyl-cyclohexanol (**3**), an α-alkyl-β-hydroxy-sulfide generated (69%) 2-methyl cyclohexanone (**3a**), and ethyl ethanethiolsulfonate (56–61%) (Sch. 2a). Nevertheless, when similar conditions were used to bisaromatic derivative **4**, benzaldehyde (**4a**) (75%) and ethylethane thiolsulfonate were obtained through an oxidative cleavage route (Sch. 2b).

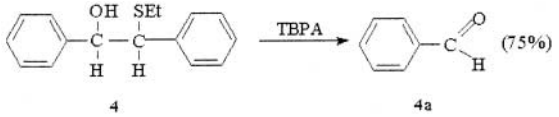
The mechanism of the chemical oxidation for the β-hydroxy-sulfides **1**, **2**, **3**, and **4** with TBPA can be suggested (Sch. 3). This way, at first, it must occur an oxidation of the sulfur atom which can lead to the corresponding sulfoxide (Sch. 3, $\mathbf{A_1}$). Then, if there is an α-alkyl-substituent or an α-phenyl substituent, the following and slowest step might be the subsequent cleavage of the carbon–sulfur bond (C–S)



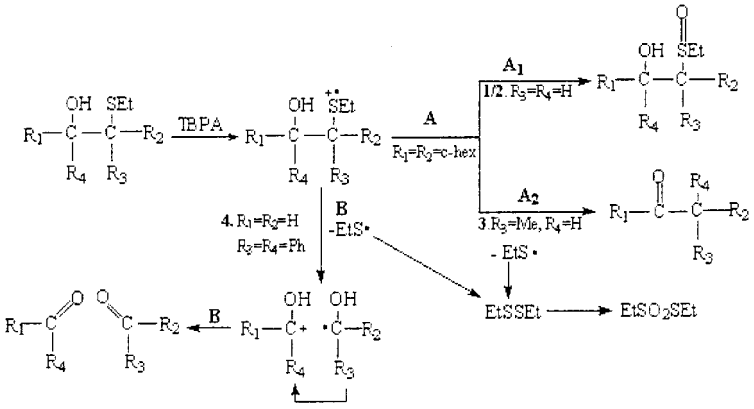
Scheme 1.



Scheme 2a.



Scheme 2b.



Scheme 3.

and a carbocationic species formation, which undergoes the pinacol-type rearrangement (Sch. 3, $\mathbf{A_2}$) for and a cleavage mechanism for **4** (Sch. 3, **B**). It is noteworthy that on the mechanism of oxidation for (similar to the pinacolinic rearrangement); heteroatoms such as nitrogen, sulfur, and selenium have ever eve been used by generating cationic intermediates to direct this kind of rearrangment.[6]

The different reactivity observed in the chemical oxidation of β-hydroxy-sulfides with TBPA in comparison to the using of generated

chloronium "in situ" can be briefly discussed. At first the known anodic potential of TBPA formation is lower, then the oxidation with TBPA might be milder, more selective, and more efficient. In fact, diastereomeric sulfoxides can be obtained in medium yields via an easy oxidative method. Besides, the common phenyl group neighboring effect, as in **4**, favors the carbon–carbon cleavage and the presence of an *alpha*-alkyl group, as in **3**, favors the pinacol-type rearrangement. Similar rearrangement occurs with α-phenyl-β-hydroxy-sulfides with generated chloronium "in situ"[6] or with α,α-bisphenylthio-β-phenyl-β-hydroxy compounds with electrogenerated TBPA.[7]

In summary, the *tris*(4-bromophenyl)aminium hexachloroantimonate (**5**) showed to be an interesting reagent to provide a sulfide diastereoselective oxidation method to sulfoxide obtaining from non α-alkyl-substituted β-hydroxy-sulfides. The observed pinacol-type rearrangement is also interesting due to the fact that it should be a selective method for oxidative ketone obtaining from or α-phenyl-β-hydroxy-sulfides using a commercial and simple reagent, the TBPA.

EXPERIMENTAL

Melting points were determined on a Mettler apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker instrument (AC-200 MHz) in $CDCl_3$ using tetramethylsilane as an internal standard. FT–IR spectra were recorded on a Mattson instrument model Galaxy 3000. The microanalysis were performed on a Perkin–Elmer 240B elemental analyzer. Chromatography was performed on SiO_2 (Merck, 70–230 mesh, Kieselgel 60).

Compounds **1–5** were obtained through the usual procedures[12,13] indicated in the Sch. 1. TBPA *tris*(4-bromophenyl)aminium hexachloroantimonate (**5**), was prepared as described starting from trisphenyl amine[14,15]; TBPA and *tris*(4-bromophenyl)amine were also purchased from Aldrich for comparison and the results were exactly the same.

Synthesis of *cis*-2-Ethylsulfanyl-cyclohexanol (1)

Preparation of *cis*-2-ethylsulfanyl-cyclohexanone[12a]: Yield 89%, light yellow oil; b.p. 107–109°C/9 torr (lit[12a]: 119–121°C/30 torr). IR ν_{max} (KBr, cm^{-1}): 170 (C=O). ^{1}H NMR ($CDCl_3$): 3.20 (m, 1H), 2.43 (q, 2H, $J = 7$ Hz), 3.20–1.30 (m, 8H), 1.20 (t, 3H, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$): 207.11, 51.40, 36.60, 32.47, 26.38, 25.11, 21.10, 13.84.

***cis*-2-Ethylsulfanyl-cyclohexanol (1):** Yield 69%, light yellow oil; b.p. 81–82°C/0.8 torr. IR ν_{max} (KBr, cm^{-1}): 3200 (O–H). ^1H NMR ($CDCl_3$): 3.20 (m, 1H), 2.43 (q, 2H, $J = 7$ Hz), 2.30 (m, 1H), 2.20–1.30 (m, 8H), 1.20 (t, 3H, $J = 7$ Hz). ^{13}C NMR $CDCl_3$) 66.81, 49.85, 33.43, 31.17, 24.53, 23.97, 20.30, 14.61. Anal. calcd. for $C_8H_{16}OS$: C 59.97, H 10.05; Found: C 59.91, H 9.98.

Preparation of *trans*-2-ethylsulfanyl-cyclohexanol (2)[12b]: Yield 59%, light yellow oil; b.p. 95–97°C/1 torr (lit[11]: 93–100°C/1 torr). IR ν_{max} (KBr, cm^{-1}): 3200 (O–H). ^1H NMR ($CDCl_3$): 3.30 (m, 1H), 2.63 (q, 2H, $J = 7$ Hz). 2.30–1.30 (m, 8H), 2.32 (m, 1H), 1.27 (t, 3H, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$): 71.81, 52.45, 32.43, 28.03, 25.75, 23.61, 20.30, 14.91. Anal. calcd. for $C_8H_{16}OS$: C 59.97, H 10.05; Found: C 59.90, H 9.94.

Synthesis of 2-Ethylsulfanyl-2-methyl-cyclohexanol (3)

Preparation of 2-chloro-2-methyl-cyclohexanone[12c]: Yield 74%, yellow oil; b.p. 90–92°C/20 torr, (lit[12c]: 90°C/20 torr). IR ν_{max} (KBr, cm^{-1}): 1730 (C=O). ^1H NMR ($CDCl_3$): 3.40–1.40 (m, 8H), 1.58 (s, 3H).

Preparation of 2-ethylsulfanyl-2-methyl-cyclohexanone: Yield 73%, light yellow oil; b.p. 53–54°C/1 torr. IR ν_{max} (KBr, cm^{-1}): 1725 (C=O). ^1H NMR ($CDCl_3$): 2.30 (q, 3H, $J = 7$ Hz), 3.40–1.60 (m, 8H), 1.40 (s, 3H), 1.15 (t, 3H, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$): 206.13, 53.04 39.81, 35.83, 26.32, 23.01, 21.50, 20.57, 13.54. Anal. calcd. for $C_9H_{16}OS$: C 62.79, H 9.30; Found: C 62.80 H 9.35.

2-Ethylsulfanyl-2-methyl-cyclohexanol (3): Yield 68%, light yellow oil; b.p. 77–78°C/1 torr. IR ν_{max} (KBr, cm^{-1}): 3200 (O–H). ^1H NMR ($CDCl_3$): 3.3. (q, 1H, $J_1 = 10$ Hz, $J_2 = 5$ Hz), 2.58 (m, 3H, 2H with D_2O), 2.00–1.10 (m, 11H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$): 73.18, 51.91, 34.94, 28.74, 24.42, 21.48, 21.04, 20.17, 14.23. Anal. calcd. for $C_9H_{18}OS$: C 62.12, H 10.40; Found: C 62.32, H 10.54.

Synthesis of 2-Ethylsulfanyl-1,2-diphenyl-ethanol (4)

Preparation of benzoin[13a]: Yield 80%, colorless crystals; m.p. 135–137°C (lit[13a]: 137°C). IR ν_{max} (KBr, cm^{-1}): 3230 (O–H), 167 (C=O). ^1H NMR ($CDCl_3$): 8.10–7.70 (m, 2H), 7.60–7.05 (m, 8H), 5.86 (s, 1H), 4.30 (s, 1H).

Preparation of desyl chloride(2-chloro-1,2-diphenyl-ethanone)[13b]: Yield 80%, colorless crystals; m.p. 64–66°C (lit[13a]: 65–66°C). IR ν_{max}

(KBr, cm^{-1}): 1680 (C=O). ^{1}H NMR ($CDCl_3$): 7.70–7.40 (m, 8H), 6.06 (s, 1H).

2-Ethylsulfanyl-1,2-diphenyl-ethanone[13]: Yield 73%, colorless crystals; m.p. 75–77°C (lit[13]: 74.1–75.5°C). IR ν_{max} (KBr, cm^{-1}): 1685 (C=O). ^{1}H NMR ($CDCl_3$): 8.05–7.60 (m, 2H), 7.60–7.05 (m, 8H), 5.46 (s, 1H), 2.46 (q, 2H, $J = 8$ Hz), 1.18 (t, 3H, $J = 8$ Hz). ^{13}C NMR ($CDCl_3$): 195.02, 136.79, 135.89, 132.89, 128.77, 128.71, 128.65, 128.44, 127.68, 55.10, 25.41, 14.09. Anal. calcd. for $C_{16}H_{16}OS$: C 75.00, H 6.25; Found: C 74.92, H 6.24.

2-Ethylsulfanyl-1,2-diphenyl-ethanol (4): Yield 83%, colorless crystals; m.p. 145–147°C. IR ν_{max} (KBr, cm^{-1}): 3320 (O–H). ^{1}H NMR ($CDCl_3$): 6.75–6.70 (m, 7H), 6.46–6.55 (m, 3H), 4.60 (d, 1H, $J = 7$ Hz), 3.76 (d, 1H, $J = 7$ Hz), 3.05–2.85 (s, 1H, absent in D_2O), 2.09 (q, 2H, $J = 8$ Hz), 1.06 (t, 3H, $J = 8$ Hz). ^{13}C NMR ($CDCl_3$): 140.95, 139.50, 129.29, 128.82, 128.39, 127.85, 127.65, 127.55, 76.89, 59.55, 25.67, 14.39. Anal. calcd. for $C_{16}H_{18}OS$: C 74.42, H 6.98; Found: C 74.54, H 6.86.

Synthesis of *tris*(4-Bromophenyl)aminium Hexachloroantimonate-TBPA (5)

Preparation of *tris*(4-bromophenyl)amine[14]: Yield 86%; light green crystals; m.p. 144–146°C (lit[14]: 144.5–146.5°C). ^{1}H NMR ($CDCl_3$): 7.30 (d, 6H), 6.85 (d, 6H). ^{13}C NMR ($CDCl_3$): 146.00, 132.49, 125.53, 116.08.

Obtention of *tris*(4-bromophenyl)aminium hexachloroantimonate (5)[15]: Yield 96%; deep blue powder; m.p. 141–142°C (decomposition). UV–Vis λ_{max} (CH_2Cl_2): 725 nm.

Chemical Oxidation of β-Hydroxy-sulfides with TBPA. Typical Procedure

To a solution of 1.0 mmol of the β-hydroxy-sulfide and 0.05 g of sodium bicarbonate in anydrous acetonitrile (5 mL) was slowly added under magnetic stirring, 2.0 mmol (for **1** and **2**) to 4.0 mmol (for **3** and **4**) of TBPA. The resultant deep blue solution became colorless and then water was added (1.0 mL). After 120 min, under magnetic stirring the reactional mixture generated a green solid (*tris*-bromophenyl-amine) and a yellow solution, which was poured into 50 mL of cold methanol; then all the brominated amine was filtered off. After the filtration, the resulting solution was poured into a saturated cold aqueous solution with NaCl, the aqueous phase was extracted with dichloromethane

(3 × 50 mL) and dried over anhydrous sodium sulfate. After the removal of solvent under reduced pressure and treatment the residue on purification by column chromatography on silica gel, using hexane/ethyl acetate (8:2 v/v) as the eluent, gave the purified products after the evaporation. All the compounds produced were characterized by ^{1}H and ^{13}C NMR and FT–IR spectra and elemental analysis.

***cis*-2-Ethylsulfinyl-cyclohexanol (1a/b):** Yield 63% (**1a** and **1b**), oil. After another chromatographic separation on SiO_2 (hexane/ethyl acetate (9:1 v/v **1a** and **1b** were isolated)). **(1a):** Yield 33%, oil. IR ν_{max} (KBr, cm^{-1}): 3300 (O–H), 1020 (S=O). ^{1}H NMR ($CDCl_3$): 4.25 (m, 1H), 4.06 (m, 1H, absent in D_2O), 2.95–2.65 (m, 3H), 2.10–1.70 (m, 4H), 1.35 (t, 3H), 1.69–1.22 (m, 4H). ^{13}C NMR ($CDCl_3$): 67.50, 60.45, 42.38, 32.80, 24.29, 19.40, 18.40, 7.05. Anal. calcd. for $C_8H_{16}O_2S$: C 54.55, H 9.09; Found: C 54.60, H 9.15. **(1b):** Yield 16%, oil. IR ν_{max} (KBr, cm^{-1}): 3300 (O–H), 1020 (S=O). ^{13}C NMR ($CDCl_3$): 64.36, 60.70, 42.58, 32.73, 24.83, 21.80, 19.35, 6.78. Anal. calcd. for $C_8H_{16}O_2S$: C 54.55, H 9.09; Found: C 54.62, H 9.16.

***trans*-2-Ethylsulfinyl-cyclohexanol (2a/b):** Yield 69% (**2a** and **2b**), oil. After another chromatographic separation on SiO_2 (hexane/ethyl acetate (9:1 v/v **2a** and **2b** were isolated)). **(2a):** Yield 35%, light yellow crystals; m.p. 43–46°C. IR ν_{max} (KBr, cm^{-1}): 3300 (O–H), 1020 (S=O). ^{1}H NMR ($CDCl_3$): 5.03 (m, 1H), 3.99 (m, 1H), 2.79–2.65 (m, 3H), 2.05–1.74 (m, 4H), 1.32 (t, 3H), 1.39–1.17 (m, 4H). ^{13}C NMR ($CDCl_3$): 71.05, 62.55, 44.08, 34.10, 24.90, 24.50, 23.40, 6.25. Anal. calcd. for $C_8H_{16}O_2S$: C 54.55, H 9.09; Found: C 54.50, H 8.95. **(2b):** Yield 18%, colorless crystals; M.p 80–82°C. IR ν_{max} (KBr, cm^{-1}): 3300 (O–H), 1020 (S=O). ^{13}C NMR ($CDCl_3$): 68.46, 63.10, 42.08, 35.33, 24.34, 23.68, 21.15, 7.51. Anal. calcd. for $C_8H_{16}O_2S$: C 54.55, H 9.09; Found: C 54.49, H 8.96.

Benzaldehyde (**4a**) (also identified as its corresponding 2,4-dinitrophenyl-hydrazone) and 2-methyl cyclohexanone (**3a**) were identified spectroscopically, in full agreement, by comparison with commercial samples (Aldrich). **3a** and **4a** were also quantified chromatographically. Ethylethanethiolsulfonate was identified by comparing to the authentic sample prepared as indicated.[15]

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