SELECTIVE AND REGIOSPECIFIC OXIDATION OF DITHIAALKANES

IN A GOLD(III) CATALYZED PHASE-TRANSFER PROCESS

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Abstract - The oxidation of dithiaalkanes has been carried on in a gold(111) catalyzed phase-transfer process. Using a higher concentration of catalyst and oxidant (procedure A) the bis(benzylthio)alkanes $Bz-S-(CH_2)_n$ -S-Bz (Bz = benzyl) were oxidized to the corresponding monosulfoxide when n = 1 and to disulfoxide [bis(benzylsulfinyl)alkanes] when n = 2, 3, 4, 5, and 8. In more diluite conditions (procedure B) high yields of monosulfoxides were obtained also in the case of n = 2 and 3 while the selectivity decreased for n = 4, 5, and 8. The oxidation of asymmetric dithiaalkanes, R-S-(CH₂)₃-S-R' (RR' = BzPh, BzCy, CyPh; Ph = phenyl, Cy = cyclohexyl), under experimental conditions B was regiospecific leading either to the formation of only one type of monosulfoxide (RR' = BzPh) or to the formation of both types of monosulfo-xides but in different yield (RR' = BzCy and CyPh); in all cases the alkylic and less hindered sulfur atom was oxidized in preference.

In previous work¹ we have reported the conditions for the catalytic oxidation of organic sulfides to sulfoxides promoted by gold(III) halides, equation 1.

The reaction time required for a quantitative oxidation was short for dialkylsulfides (1-7 h), quite long for alkylarylsulfides (ca. 60 h) and extremely long for diarylsulfides. Under the same experimental conditions, but in the absence of catalyst, the oxidation was negligibly small either for dialkylsulfides (1-3 %) or for alkylarylsulfides (< 20 %).

One point of interest was that the oxidation accomplished by this procedure took place selectively at the sulfur atom even in the presence of other oxidizable groups such as vinyl, 'tertiary amino, hydroxy, and diol in the side chains of the sulfide.

We have now extended this procedure to

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		experi	experimental conditions \underline{A}			experimental conditions B					
1	n	reaction time (min)	<u>2</u> yield (%)	<u>3</u>	yteld (%)	reaction time (min)	<u>2</u>	yield (%)	<u>3</u>	yield (%)	
<u>la</u> ⁶	1	480	<u>2a</u> ² 87		~	200 (h)	<u>2a</u>	84		-	
<u>1b</u> 6	2	30	-	<u>3b</u> *	92	25	<u>2b</u>	79	<u>3b</u>	18	
<u>1c</u> ⁶	3	60	-	<u>3c</u>	94	80	<u>2c</u>	67	<u>3c</u>	16	
<u>1d</u> '	4	120	-	<u>3d</u>	92	140	<u>2d</u>	44	<u>3d</u>	26	
<u>le</u>	5	120	-	<u>3e</u>	89	170	<u>2e</u>	45	<u>3e</u>	27	
<u>1f</u>	8	120	-	<u>3f</u>	93	200	<u>2f</u>	49	<u>3f</u>	23	

the oxidation of dithiaalkanes having either different substituents at the sulfur atoms $[R-S-(CH_2)_3-S-R'; RR' = BzPh, BzCy, and$ CyPh; Bz = benzy!, Cy = ciclohexy!, Ph = pheny!] or different chain length between the two atoms of sulfur $[Bz-S-(CH_2)_n-S-Bz;$ n = 1, 2, 3, 4, 5, and 8].

In the case of bis(benzylthio)alkanes the oxidation reaction led to the exclusive formation of monosulfoxide only in the case of Bz-S-CH₂-S-Bz, in all other cases both mono- and di-sulfoxide [bis(benzylsulfinyl)alkanes] were formed simultaneously, the relative yield being dependent upon several



Table 2. Oxidation products of asymmetric sulfides under experimental conditions B.



factors including the value of n, the concentration of catalyst and oxidant, and the reaction time. Thus we have performed the oxidation reaction under two standard experimental conditions, A and B. A denotes stronger oxidation medium [per mol of substrate: 0.1 mol of $(Bu_4N^{\dagger}AuCl_{4})$, 10 mol of HNO3 (10 % in water), CH3NO2 half the volume of the aqueous phase]; <u>B</u> denotes milder conditions [per mol of substrate: 0.05 niol of $(Bu_4N^+AuCl_4^-)$, 5 mol of HNO3 (5 % in water), CH3NO2 half the volume of the aqueous phase]. The oxidation products obtained in the case of symmetric sulfides under the experimental conditions A and B are summarized in table 1; those obtained in the oxidation of asymmetric sulfides under the experimental conditions B are reported in Table 2.

The symmetric sulfides Bz-S-(CH₂)_n-S-Bz, with the only exception of that with n = 1, under the experimental conditions <u>A</u>, were oxidized quantitatively (89-94% yield) to the corresponding bis(benzylsulfinyl)alkanes in a relatively fast process (0.5-2.0 h reaction time). On the contrary Bz-S-CH₂-S-Bz was oxidized to the corresponding monosulfoxide in a slow process (87 % conversion after 8 h reaction), moreover by prolongating the reaction time, no further oxidation to disulfoxide was observed (a similar behaviour was also observed in the oxidation of this substrate by traditional reagents).²

A noticeable degree of selectivity was encountered performing the reaction under conditions <u>B</u>. The monosulfoxide was, in fact, the predominant product also in the case of n = 2 and 3, while the selectivity decreased for n = 4, 5, and 8. As expected the bis(benzylthio)methane with n = 1 was oxidized exclusively to the corresponding monosulfoxide, but, the process was even slower than that carried on under conditions A.

As matter of fact the reaction rate was

very much dependent upon the value of n (in Figure 1 we have reported the decrease in concentration of the starting substrate as a function of time under experimental conditions B). It can be noticed how the rate decreases steeply by increasing the value of n. The Bz-S-CH2-S-Bz does not follow the general trend and is by far the less reactive with an half life of 1 d. These data are important in relation to the reaction mechanism. In a previous kinetic study on the oxidation of monosulfides by gold(111) chloride it was pointed out that the intermediate [AuCl4-xLx] species, in which some Cl ions had been substituted by sulfide molecules (L), were more reactive towards the redox process. This latter occurred through an atom-transfer process involving the metal substrate and an extra, not coordinated, molecule of sulfide. On these bases we would expect the dithiaalkanes to give rise to faster processes than monosulfides, as indeed has been found. In fact one can easily realize that these molecules can either behave as bidentate towards the metal centre, giving rise to the formation of intermediate species with higher x, or act as monodentate towards the metal while the second, uncoordinated, sulfur atom interacts with the chloride promoting the redox process which therefore would not require the partecipation of an external molecule of sulfide. Probably both activation mechanisms can operate depending upon the value of n; this could explain why also the dithiaalkane with n = 8, which can hardly behave as bidentate towards the same metal, is more reactive than simple monosulfides. However a more complete and thorough kinetic study is required for a full understanding of all mechanistic details occurring in the oxidation of dithiaalkanes by gold(111).

Concerning the asymmetric sulfides we can notice (Table 2) how under conditions <u>B</u> the oxidation of $Bz-S-(CH_2)_3-S-Ph$ was completely regiospecific leading to the formation of the monosulfoxide in which only the more reactive Bz-S-group had been oxidized. A smaller degree of regioselectivity was observed in Bz-S-(CH₂)3-S-Cy where the two sulfide function both linked to an alkyl groups, differ for the bulkyness of the substituents and the less hindered Bz-S-mojety is oxidized in preference. in the case of Cy-S-(CH2)3-S-Ph the reactivities of two this groups, both disactivated, one sterically and the other electronically, are compared. After 2 h reaction both types of monosulfoxides were formed (in 57 and 36 % yield for Cy-S(=0)-(CH2)3-S-Ph and Cy-S-(CH2)3 -S(=0)-Ph respectively); however by prolongatin the reaction time (4 h) only one of the two isomers, Cy-S-(CH₂)₃-S(=0)-Ph, was oxidized further to Cy-S(=0)-(CH₂)₃-S(=0)-Ph allowing the formation of only one type of monosulfoxide

In conclusion the oxidation of symmetric sulfides $(\underline{1a-f})$ carried out in experimental conditions <u>B</u> is significantly selective and allows the formation of monosulfoxides in better yield than that obtained using traditional oxidizing agents, as bromine,⁴ (this reagent is to be avoided in the oxidation of Bz-S-CH₂--S-Bz where it rise to the formation of a complex reaction mixture). Similarly the oxidati under conditions <u>B</u> of asymmetric sulfides $(\underline{4}, \underline{6}, \text{ and } \underline{9})$ is regiospecific allowing either the obtainment of only one type of monosulfoxic or the formation of both types of monosulfoxide but in different yield.

EXPERIMENTAL

Equipment. M.p.s are uncorrected and were determined with a Buchi apparatus. ¹H-NMR and MS spectra were recorded with a Varian EM-390 spectrometer (TMS internal standard) and a Hewlett-Packard HP 5980A spectrometer equipped with a Data System 5870A respectively IR spectra were recorded as films or in nujol muil with a Perkin-Elmer Model 337 and Model 297 grating spectrophotometer.

Analytical liquid chromatography was performed on a Waters Associates ALC/GPC--202/R 401 chromatograph (Waters Associates, Milford, M.A., U.S.A.) equipped with a U6K universal injector, a Model M6000 and M-45

	COMPOUND	м,р, ^а (°С)]R ^b (cm ⁻¹)	¹ H-NMR (CDC1 ₃) δ (ppm)
<u>le</u>	Ors: (CH2)5 5 O	011	1600, 1490, 695 ^C	7.40-7.15 (m, 10 H), 3.65 (s, 4+H), 2.40 (t, 6.75Hz, 4 H), 1.65-1.35 (m, 6 H).
Щ	Q_2_(CH ⁵) ^{8,2} _Q	38-9 ^d	1600, 1495, 700 ^C	7.40-7.15 (m. 10 H), 3.65 (s. 4 H), 2.40 (t. 7.05Hz, 4 H), 1.70-1.10 (m. 12 H).
<u>2P</u>	0~s~ ^s ~ ^{\$}	98-9	1030, 775,-705	7.25 (m, 10 H), 3.86 (q, J _{AB} =13.5Hz, 2 H), 3.64 (s, 2 H), 2.70 (m, 4 H).
<u>2c</u>		78-9	1035, 770, 705	7,27 (m, 10 H), 3.86 (q, JAB+13.5Hz, 2 H), 3.62 (s. 2 H), 2.70-2.40 (m, 4 H), 2.20-1.80 (m, 2 H).
59	Ø_;Q	73-4	1025, 775, 705	7.28 (m, 10 H), 3.90 (q. J _{AB} -13.5Hz, 2 H), 3.63 (s. 2 H), 2.70-2.30 (m, 4 H), 1.90-1.50 (m, 4 H).
<u>2e</u>	0~5 ^{-(CH2)5-5} 0	75-6	1030. 770. 705	7.30 (m, 10 H), 3.95 (q, J _{AB} +13.5Hz, 2 H), 3.68 (s, 2 H), 2.70-2.30 (m, 4 H}, 1.90-1.20 (m, 6 H).
<u>2f</u>		77-8	1020, 770, 700	7.30 (m, 10 H), 3.90 (q, J _{AB} =13.5Hz, 2 H), 3.65 (s, 2 H), 2.70-2.30 (m, 4 H), 1.90-1.20 (m, 12 H).
<u>3b</u>	0^ <u>s</u> ~ <u>s</u> _0	194-6	1027, 775, 705	7.34 (m, 10 H), 4.00 (q, J _{AB} =13.5Hz, 4 H), 3.20-2.80 (m, 4 H).
<u>3c</u>		184-6 ^d	1045, 780, 705	7.34 (m. 10 H), 3.98 (q, J _{AB} =13.5Hz, 4 H), 2.80-2.60 (m. 4 H), 2.50-2.10 (m. 2 H).
30	0~;~~ ^{;_0}	169-72	1030, 775, 705	7.33 (m, 10 H), 3.97 (q, J _{AB} =13.5Hz, 4 H), 2.58 (m, 4 H), 1.87 (m, 4 H).
<u>3e</u>	$\bigcirc \widehat{\mathbf{S}}_{0}^{s} \widehat{\mathbf{C}}_{2}^{c} \widehat{\mathbf{S}}_{0}^{s} \widehat{\mathbf{O}}$	160-2	1035, 775, 705	7.33 (м, 10 Н), 3.97 (q, J _{AB} =13.5Hz, 4 К), 2.57 (m, 4 Н), 4.70 (м, 6 Н).
<u>3f</u>	O 5 (CH2)8 5 O	149-51 ^d	1020, 770, 700	7.33 (m, 10 H), 3.95 (q, J _{AB} =13.5Hz, 4 H), 2.70-2.40 (m, 4 H), 1.90-1.20 (m, 12 H).
<u>6</u>	Q~,~~,~Q	011	1600, 1260, 700 ^C	7.40-7.15 (m, 5 H), 3.68 (s, 2 H), 2.70-2.38 (m, 5 H), 2.10-1.10 (m, 12 H).
2	Ori~s~	54-5	1050, 770, 700	7.30 (m, 5 H), 3.90 (q, Jдg=13,0Hz, 2 H), 2.80-2.50 (m, 5 H), 2.10-1,20 (m, 12 H).
<u>8</u>	Or s~ sol	oi1	1040, 770, 710 ^C	7.27 (m, 5 H), 3.65 (s, 2 H), 2.70-2.40 (m, 5 H), 2.10- -1.20 (m, 12 H).
<u>9</u>	Ø ^{s~s} D	110	1585, 1260, 690 [°]	7.45-7.10 (m, 5 H), 3.00 (t, 6.9Hz, 2 H), 2.62 (t, 6.9Hz, 2 H), 2.55 (m, 1 H), 2.10-1.00 (m, 12 H).
<u>10</u>	$a_{i}^{i} \sim c$	oil	1040, 740, 695 ^C	7.28 (m, 5 H), 3.04 (t, 6.75Hz, 2 H), 2.80-2.30 (m, 3 H), 2.13 (m, 2 H). 1.90-1.20 (m. 10 H).
<u>11</u>	$\mathbb{Q}^{s}_{s} \sim {}^{s}_{s} \mathcal{O}$	42-3	1045, 750, 690 ^C	7.53 (m, 5 H), 3.10-2.80 (m, 2 H), 2.70-2.30 (t, 7.05Hz, 2 H, plus m, 1H), 2.10-1.20 (m, 12 H).
12	\bigcirc ⁱ \sim ⁱ \bigcirc	93-5	1045, 760, 700	7.55 (m, 5 H), 3.05 (m, 2 H), 2.90-2.30 (m, 2 H, plus m, 1 H), 2.20 (m, 2 H), 1.90-1.10 (m, 10 H).

a) Unless otherwise noted, products were recrystallized from CH_2Cl_2 - nexame mixtures b) Unless otherwise reported, spectra were registered in nuiol

c) Liquid film

d) Recrystallized from methanol - water mixture

solvent delivery systems, a Model 480 λ max differential UV detector and a Model 401 refractive index (RI) detector.

Analytical data (% C, H, N, and S) were obtained from Mikroanalytisches Laboratorium, Dr. H. Pascher, Bonn (Germany).

Reagents. (BuaN AuCla) was prepared according to the reported procedure¹; (Bu₄N⁺ HSO4 (Tetrabutylammonium hydrogen sulfate) and HAuCl4 were purchased from Fluka and

from Ventron Corp. respectively and were used without further purification. The symmetric . sulfides Bz-S-(CH2)n-S-Bz: 1a (n=1), 1b (n=2), 1c (n=3), 1d (n=4), 1e (n=5), and 1f (n=8), were prepared by reaction of the corresponding dibromoalkane with benzylmercaptan in phase transfer conditions (PTC).⁵ The asymmetric sulfides R-S-(CH2)3-S-R': 4 (RR'=BzPh), 6 (RR'=BzCy), and 9 (RR'=CyPh), were prepared by selective displacement reactions of 1,3-di-

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bromopropane with the corresponding mercaptans.⁵

Table 3 contains some characteristics of the newly synthesized sulfides, while physico--chemical and spectroscopical data, of $\underline{1a-c}^{6}$, $\underline{1d}^{7}$, and $\underline{4}^{9}$ were us reported in literature.

Oxidation reaction: Procedure A. The sulfide (5 mmol) dissolved in nitromethane (16 cm^3) was treated with nitric acid (10 % in water, 32 cm³, 50 mmol) in the presence of (Bu, N⁺AuCl,) (0.50 mmol). After stirring for the time required, the reaction mixture was extracted with dichloromethane washed with a saturated acqueous solution of sodium thiosulfate to eliminate the catalyst, dried over Na₂SO₄ and evaporated under reduced pressure. The solid residue was chromatographed on an open column of silica gel (Si60, 0.040-0.063 mm) eluting with ethylacetate / methanol (90/10, v/v). The purity of the compounds was checked by HPLC. Procedure B. The sulfide (5 mmol)-dissolved in nitromethane (16 cm^3) was treated with nitric acid (5 % in water, 32 cm³, 25 mmol) in the presence of $(Bu_A N^{+} AuCl_{4}^{-})$ (0.25 mmol). After stirring for the time required the reaction mixture was worked up as described above. The crude material was then chromatographed on an open column of silica gel (Si60, 0.040-0.063 mm) eluting with:

- a) n-hexane/ethylacetate (90/10, v/v) to separate the starting sulfides;
- b) n-hexane/ethylacetate (50/50, v/v) to separate the monosulfoxides;
- c) ethylacetate/methanol (90/10, v/v) to separate the disulfoxides.

Reaction progress in the oxidation of symmetric sulfides under experimental conditions <u>B</u> was monitored by prelevating samples of the reaction mixture (organic phase) at fixed intervals and processing them: the crude materials were analyzed by ¹H-NMR and HPLC (column: LiChrosorb CN, 10 μ , 25 cm; Mobile Phase: linear gradient from 70 % n-hexane : 30 % chloroform (v/v) to 50 % acetonitrile : 50 % chloroform (v/v) in 10 min; temp. amb.; flow rate: 2.0 ml/min, det. 254 nm UV).

The yields given in Tables refer to pure isolated species. Table 3 collects some characteristics of the newly synthesized sulfides and sulfoxides.

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