Tetrahedron Vol 39, No 19, pp 3181 to 3184, 1983
Printed in Great Britain

0040-4020/83 $3.00 + .00
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GOLD(III) CATALYZED OXIDATION OF SULFIDES TO SULFOXIDES BY NITRIC ACID UNDER PHASE-TRANSFER CONDITIONS: A NEW SYNTHESIS OF SULFOXIDES

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(Received in UK 27 January 1983)

Abstract—Gold(III) halides catalyze the oxidation of sulfides to sulfoxides in a phase-transfer process. The organic sulfides, dissolved in nitromethane, are treated with ($Bu_4N^+AuCl_4^-$) in catalytic amount and aqueous nitric acid which acts as oxidant. The oxidation of the thio-group is selective and can be carried out also in the presence of other oxidizable groups, such as vinyl, tertiary amino, hydroxy, diol etc, which are left unchanged. Moreover in the case of asymmetric disulfides the reaction is regiospecific leading to the formation of a single monosulfoxide.

Gold(III) halides have been known from many years to oxidize organic sulfides to sulfoxides and sulfones[1-3] and, more recently, the redox process has been studied from a kinetic point of view.[4,5] The above process for the oxidation of a sulfide to sulfoxide is, according to the following eqn (1),:

$$R{-}S{-}R' + AuCl_4^- + H_2O \rightarrow R{-}\overset{\overset{O}{\|}}{S}{-}R' + AuCl_2^- + 2HCl$$

R, R'=Alkyl group. (1)

However, until now, the oxidizing Au(III) species have been used in stoichiometric amounts and no attempts to find the conditions for a catalytic process have been carried out. Moreover its use as an oxidizing agent has been reported only in a few examples.

Satisfactory results have been obtained performing the redox reaction in phase-transfer conditions. The two phases employed were aqueous nitric acid and nitromethane. The catalyst (0.02–0.05 mole per mole of sulfide) can be added as ($Bu_4N^+AuCl_4^-$) salt or as a 1:1 mixture of $H[AuCl_4]$ and ($Bu_4N^+HSO_4^-$).

The redox process that occurs in the organic phase or at the interface is in agreement with the general eqn (2):

$$(Ar)R{-}S{-}R' \xrightarrow[CH_3NO_2/HNO_3\ 10\%,\ r.t.]{Au(III)\ catalyst} (Ar)R{-}\overset{\overset{O}{\|}}{S}{-}R' \quad (2)$$

Ar=Aryl group
R, R'=Alkyl group

while at the nitromethane–water interface and/or in water the colourless Au(I) species are reoxidized to the yellow Au(III) species according to eqn (3):

$$2NO_3^- + 3AuCl_2^- + 6Cl^- + 8H_3O^+ \rightarrow 3AuCl_4^- + 2NO + 12H_2O. \quad (3)$$

Since the oxidation of the organic sulfide by Au(III) is generally faster than the oxidation of Au(I) by nitric acid, the reaction mixture was colourless until all the sulfide was oxidized to sulfoxide and became yellow (Au(III) species) when the reaction was over.

The working up of the mixture was carried out by extraction with dichloromethane, washing of the resulting solution with a saturated aqueous solution of sodium thiosulfate to eliminate the catalyst, drying over sodium sulfate, and distilling. The yields were generally high, ranging from 82 to 97% and the amount of side products was negligible.

All the sulfides examined in this work together with the reaction time and yields, are summarized in Table 1. Furthermore, in Table 2 m.p's and spectroscopical data of the unknown sulfoxides are reported.

In the first place the hypothesis that ($Bu_4N^+NO_3^-$) could have a catalytic activity was ruled out by substituting in the reaction ($Bu_4N^+AuCl_4^-$) with ($Bu_4N^+HSO_4^-$), which does not show any catalytic effect.

Moreover, ($Bu_4N^+Br^-$) allows sulfide-sulfoxide transformation in appreciable amount for the easy oxidability of the Br^- to Br_2. Actually, the system ($Bu_4N^+Br^-$)/Br^- in presence of nitric acid is not selective for the oxidation of the sulfides and gives very often mixtures of compounds.

The choice of the organic solvent is of particular importance. Nitromethane only was found suitable, giving rise to a relatively fast reaction rate at room temperature, while solvents such as dichloromethane, chloroform, some ethers, etc had to be discarded. This

Table 1. Phase-transfer catalyzed oxidation of sulfides with nitric acid

Substrate	Product[a]	Reaction time (h)	Yield (%)[b,c]
(1) $C_6H_5CH_2$–S–$CH_2C_6H_5$	(1')[6] $C_6H_5CH_2$–S(=O)–$CH_2C_6H_5$	2	94 (1)
(2) $CH_3(CH_2)_3$–S–$(CH_2)_3CH_3$	(2')[6] $CH_3(CH_2)_3$–S(=O)–$(CH_2)_3CH_3$	1	92
(3) $CH_3(CH_2)_7$–S–$(CH_2)_7CH_3$	(3')[7] $CH_3(CH_2)_7$–S(=O)–$(CH_2)_7CH_3$	1	97 (3)
(4) $(CH_3)_2CH$–S–$CH(CH_3)_2$	(4')[8] $(CH_3)_2CH$–S(=O)–$CH(CH_3)_2$	7	92
(5)[9] $C_6H_5CH_2$–S–$(CH_2)_2COCH_3$	(5') $C_6H_5CH_2$–S(=O)–$(CH_2)_2COCH_3$	2	86 (3)
(6)[10] $C_6H_5CH_2$–S–$CH_2CH{=}CH_2$	(6')[11] $C_6H_5CH_2$–S(=O)–$CH_2CH{=}CH_2$	6	82
(7)[12] $C_6H_5CH_2$–S–$(CH_2)_2COOH$	(7')[13] $C_6H_5CH_2$–S(=O)–$(CH_2)_2COOH$	4	85
(8)[14] $C_6H_5CH_2$–S–CH_2CH_2OH	(8')[15] $C_6H_5CH_2$–S(=O)–CH_2CH_2OH	3	89 (3)
(9)[16] $C_6H_5CH_2$–S–$CH_2CH_2OCOCH_3$	(9') $C_6H_5CH_2$–S(=O)–$CH_2CH_2OCOCH_3$	5	87 (2)
(10)[17] $C_6H_5CH_2$–S–$(CH_2)_2CH_2Br$	(10') $C_6H_5CH_2$–S(=O)–$(CH_2)_2CH_2Br$	4	89
(11)[18] $C_6H_5CH_2$–S–$CH_2CHOHCH_2OH$	(11') $C_6H_5CH_2$–S(=O)–$CH_2CHOHCH_2OH$	4	76
(12)[19] $C_6H_5CH_2$–S–$(CH_2)_2N(C_2H_5)_2$	(12') $C_6H_5CH_2$–S(=O)–$(CH_2)_2N(C_2H_5)_2$	70	82
(13) $C_6H_5CH_2$–S–$(CH_2)_2NHCOOBz$	(13') $C_6H_5CH_2$–S(=O)–$(CH_2)_2NHCOOBz$	18	82
(14) 	(14')[20] 	2	93
(15) $C_6H_5CH_2$–S–C_6H_5	(15')[21] $C_6H_5CH_2$–S(=O)–C_6H_5	60	89 (18)
(16)[7] C_6H_5–S–$(CH_2)_9CH_3$	(16')[7] C_6H_5–S(=O)–$(CH_2)_9CH_3$	60	94 (20)
(17)[22] $C_6H_5CH_2CH_2$–S–C_6H_5	(17') $C_6H_5CH_2CH_2$–S(=O)–C_6H_5	60	92 (24)
(18)[23] $C_6H_5CH_2$–S–$(CH_2)_3$–S–C_6H_5	(18') $C_6H_5CH_2$–S(=O)–$(CH_2)_3$–S–C_6H_5	2	97

a) All products give satisfactory microanalyses (C, ±0.33; H, ±0.27; N, ±0.27; S, ±0.33). The spectroscopic data (IR, ^{1}H-NMR, mass spectra in chemical ionization) are in agreement with the proposed structures and, when reported, with the literature data.
b) Yields are calculated on the starting sulfides and are given on pure isolated products. The purity was checked by analytical HPLC.
c) Numbers in brackets show the yield obtained when the reaction was carried out in the same conditions but in absence of ($Bu_4N^+AuCl_4^-$).

fact can be probably explained taking into account the high dielectric constant and water uptake of nitromethane.

The nature of the starting sulfides controls both the activity of the Au catalyst and the reaction rate. The reaction time, determined in the presence of Au-catalyst, results for dialkylsulfides (1–7 hr) much shorter than for alkylarylsulfides (*ca* 60 hr) and is extremely long for diarylsulfides. Moreover the reaction rate is very sensitive to steric factors being much faster for unhindered substrates than for hindered ones. When the reaction is carried out in the same conditions but in absence of Au-catalyst ($BuN^+AuCl_4^-$) the dialkylsulfides are converted into the corresponding sulfoxides to a slight extent (1–3%), while alkylarylsulfides show a higher degree of conversion (18–24%).

The oxidation accomplished by the above procedure takes place selectively at the S atom even if other oxidizable groups such as vinyl, tertiary amino, hydroxy, diol, etc. are present together with the sulfide function. Some additional relationships between chemical structure and reactivity can be deduced on the basis of the results obtained.

Compound **12** shows a reaction rate much lower than that of other dialkylsulfides indicating that the presence of the amino group produces a strong deactivating effect; on the other hand when an amide function is present, as in compound **13**, this effect appears to be smaller.

For the compound BzPh(CN)C—S—Bz, both electronic and steric effects hinder the oxidation reaction and, in our experimental conditions, the starting sulfide can be quantitatively recovered after *ca* 20 hr.

Table 2. Characterization of the unknown sulfoxides

Sulfoxides	M.p.[a] (°C)	IR[b] (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
5'	101–102	1700, 1020, 770, 700	7.32 (bs, 5H, $-C_6\underline{H}_5$), 3.93 (q, 2H, AB, J_{AB}= 13.0Hz, $-SO-C(\underline{H}_A)(\underline{H}_B)C_6H_5$); 2.87 (m, 4H, $-(C\underline{H}_2)_2-$), 2.12 (s, 3H, $C\underline{H}_3CO-$)
9'	67–68	1700,1220, 1025, 770,700	7.35 (bs, 5H, $-C_6\underline{H}_5$), 4.65–4.35 (m, 2H, ABX_2, $-C\underline{H}_2OAc$), 4.03 (q, 2H, AB, J_{AB} = 13.0 Hz, $C_6H_5C\underline{H}_2SO-$), 3.10–2.70 (m, 2H, ABX_2, J_{AB} = 14.0 Hz, $-SOC\underline{H}_2CH_2OAc$), 2.03 (s, 3H, $C\underline{H}_3COO-$)
10'	72–73[c] (dec)	1030, 775,700	7.33 (bs, 5H, $-C_6\underline{H}_5$), 3.95 (q, 2H, AB, J_{AB} = 13.0 Hz, $C_6H_5C\underline{H}_2-SO-$), 3.45 (t, 2H, J = 6.0 Hz, $-C\underline{H}_2-Br$), 2.90–2.55 (m, 2H, $-SO-C\underline{H}_2(CH_2)_2Br$), 2.50–2.10 (m, 2H, $-CH_2-C\underline{H}_2-CH_2Br$)
11'	73–75 (dec)	3400, 1020, 1600, 770, 700	7.30 (bs, 5H, $-C_6\underline{H}_5$), 5.03 (bs, 1H, $-O\underline{H}$, D_2O exchange), 4.57 (bs, 1H, $-C\underline{H}$, D_2O exchange), 4.20–3.90 (m, 3H, $C_6H_5C\underline{H}_2SCH_2-C\underline{H}-OH$), 3.60–3.40 (m, 2H, $-C\underline{H}_2OH$), 2.80 (m, 2H, $-SC\underline{H}_2\underline{C}HOH$)[d]
12'	(oil)	1045, 1600, 770, 700[e]	7.34 (bs, 5H, $-C_6\underline{H}_5$), 4.02 (q, 2H, AB, J_{AB} = 13.0 Hz, $C_6H_5C\underline{H}_2SO-$), 2.90–2.65 (m, 4H, $-SOCH_2C\underline{H}_2-N\langle$), 2.50 (q, 4H, J = 7.0 Hz, 2 $CH_3C\underline{H}_2-$), 0.98 (t, 6H, J = 7.0 Hz, 2 $C\underline{H}_3CH_2-$)
13'	108–110	3340, 1695, 1280, 1025, 750, 705	7.30 (bs,10H, 2 $C_6\underline{H}_5-$), 6.02 (bs, 1H, $-N\underline{H}-$, D_2O exchange), 5.05 (s, 2H, $C_6H_5-C\underline{H}_2-O-$), 3.93 (m, 2H, $C_6H_5-C\underline{H}_2-SO-$), 3.57 (bt, 2H, J = 6.0 Hz, $-C\underline{H}_2-NH-$), 3.10–2.50 (m, 2H, $-SOC\underline{H}_2CH_2$)
17'	(oil)	1040, 750, 700[e]	7.70–7.40 (m, 5H, $C_6\underline{H}_5-SO-$), 7.30–7.07 (m, 5H, $C_6\underline{H}_5CH_2-$), 3.20–2.80 (m, 4H, $-C\underline{H}_2C\underline{H}_2-$)
18'	89–90	1030, 770, 740, 700	7.40–7.20 (m, 10H, 2 $C_6\underline{H}_5-$), 3.90 (q, 2H, AB, J_{AB} = 14.0 Hz, $C_6H_5CH_2-SO-$), 2.98 (t, 2H, J = 7.0 Hz, $C_6H_5SC\underline{H}_2-$), 2.85–2.50 (m, 2H, $-SOC\underline{H}_2CH_2-$), 2.30–1.90 (m, 2H, $-CH_2C\underline{H}_2CH_2-$)

a) Unless otherwise noted, products were recrystallized from CH_2Cl_2–hexane mixtures
b) Unless otherwise reported, spectra were registered in Nujol
c) The compound, recrystallized from methanol–water, resulted particularly unstable
d) ^{1}H-NMR (D_2O) δ : 7.50–7.40 (bs, 5H, $-C_6\underline{H}_5$); 4.40–4.10 (m, 3H, $C_6H_5-C\underline{H}_2-SO-CH_2-C\underline{H}OH$), 3.80–3.60 (m, 2H, $-C\underline{H}_2OH$), 3.20–2.80 (m, 2H, $-SOC\underline{H}_2\underline{C}HOH$) ppm.
e) Liquid film.

When the oxidation reaction is applied to disulfides, different results are obtained depending on the relative position of the two S atoms. Cyclic dithioketals, for example 3-cholestanone ethylenthioketal or phenyl-2-propanone ethylenthioketal do not undergo oxidation at the S atom: on the contrary, a quantitative regeneration of the corresponding ketone, through a 4–5 hr hydrolysis, occurs. The phenylacetaldehyde ethylenthioketal behaves similarly and the hydrolysis is complete in 15 hr.

In the case of disulfides, such as dithiane (**14**) or the dithioether **18**, the formation of a monosulfoxide in 93–97% yield takes place. Particularly, the reaction of the latter is regioselective, leading to the oxidation only at the benzylic S atom. Otherwise, with the majority of the oxidizing agents, both mono- and disulfoxide were obtained in comparable yields.

It is our aim to extend this reaction to other organic substrates paying particular attention to the factors which can determine the selectivity and the regiospecificity of the redox process.

EXPERIMENTAL

Equipment. M.ps are uncorrected and were determined with a Buchi apparatus. ^{1}H-NMR and MS spectra were recorded with a Varian EM-390 spectrometer (TMS internal standard) and a Hewlett-Packard HP5980A spectrometer equipped with a Data System 5870A. IR spectra were recorded as films or in nujol mull with Perkin-Elmer Model 337 and Mod. 297 grating spectrophotometers.

Analytical liquid chromatography was performed on a Waters Associates ALC/GPC-202/R 401 chromatograph (Waters Associates, Milford, MA, U.S.A.) equipped with a U6K universal injector, a Model M6000 and M-45 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. ($Bu_4N^+HSO_4^-$)(Tetrabutylammonium hydrogen sulfate) and $HAuCl_4$ were purchased from Fluka and from Ventron Corp. respectively and were used as such. The starting sulfides **1**, **2**, **3**, **4**, **14**, **15** are commercially available and were used without further purification. Sulfides **5–12**, **16–18** were prepared according to cited refs.

Preparation of N-benzyloxycarbonyl-2-phenylmethylthio-ethylamine (**13**). 2-Phenylmethylthio-ethylamine[24] (1.00 g, 5.99 mmol) reacted with benzylchloroformate (1.022 g, 5.99 mmol) following the Schotten-Bauman procedure.[25] The mixture was extracted with CH_2Cl_2, the organic layer washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallized from MeOH/water; yield: 1.57 g (87%); m.p. 32–33°. IR (liquid film): 3340, 1730, 1520, 1250, 750, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.50–7.10 (m, 10H, 2-C_6H_5), 5.35 (bt, 1H, -NHCOOBz), 5.05 (s, 2H, $-COOCH_2C_6H_5$), 3.60 (s, 2H, $C_6H_5CH_2S-$), 3.40–3.10 (m, 2H, $-SCH_2CH_2NH-$), 2.45 (t, 2H, $-SCH_2CH_2NH-$) ppm. (Found: C, 67.68, H, 6.39; N, 4.60; S, 10.40. $C_{17}H_{19}NSO_2$ requires: C, 67.77; H, 6.37; N, 4.64; S, 10.64%).

Preparation of ($Bu_4N^+AuCl_4^-$). To a soln of tetrachloroauric acid (7.60 mmol) in a 1M HCl (200 ml), CH_2Cl_2 (200 ml) and Bu_4NH_4Cl (15.00 mmol) were added. After 1 hr stirring the organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue was recrystallized from CH_2Cl_2/hexane. (Found: C, 32,80; H, 2.40; N, 6.30; Cl, 24.70. ($Bu_4N^+AuCl_4^-$) requires: C, 33.06; H, 2.41; N, 6.24; Cl, 24.40%).

Preparation of sulfoxides. All sulfoxides were prepared following the same procedure. In a typical experiment the sulfide (5 mmol) was dissolved in nitromethane (8 ml) and treated with HNO_3aq (16 ml, 25.00 mmol, 1.55 mol/dm^3) in the presence of the tetrabutylammonium salt of Au(III) tetrachloride (0.25 mmol). The colourless mixture was left under energic stirring until it became yellow again, then it was extracted with CH_2Cl_2 (in the case of basic substrate this step must be preceded by neutralization with Na_2CO_3 washed with a sat. $Na_2S_2O_3$ to eliminate the catalyst, dried over Na_2SO_4 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:

(a) EtOAc/cyclohexane (50/50, v/v) for compounds: **1'–3', 4', 6', 9', 10', 14'–18'**

(b) EtOAc 100% for compounds: **5', 12', 13'**

(c) EtOAc/MeOH (90/10, v/v) for compounds: **7', 8', 11'.**

The purity of the compounds was checked by HPLC in normal phase (Column: Hibar Si60, 10μ, 25 cm) or in reverse phase (Column: Hibar RP2, 10 μ, 25 cm).

Acknowledgement—We thank Dr. Giovanna Cancelliere for her technical assistance, and the National Research Council (C.N.R.) for financial support.

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