Monatshefte für Chemie 137, 307–310 (2006)
DOI 10.1007/s00706-005-0430-8

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Oxidation of Thiols to Disulfides with Molecular Oxygen in Subcritical Water

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Received June 27, 2005; accepted (revised) July 27, 2005

Summary. Molecular oxygen is used as an efficient oxidant for the oxidative coupling of thiols to disulfides in subcritical water in the absence of catalysts. The procedure utilizes water and does not require support materials and metal salts providing high yields (>90%).

Keywords. S–S Coupling; Thiols; Disulfides; Subcritical water; Molecular oxygen.

Introduction

Thiols and disulfides are important in living cells being a structural feature of many biomolecules including proteins. In many biochemical redox reactions they are interconverted [1]. In addition, disulfides play important roles in chemical processes [2]. Oxidation of thiols is the most exploited method for disulfide synthesis mainly because a large number of thiols are commerically available and/or easily synthesized. Reagents such as Ce(IV) salts [3], permanganates [4], Bi(III) nitrate pentahydrate [5], air in combination with transition metal catalysts [6], 2,6-dicarboxypyridinium chlorochromate [7], quinolinium fluorochromate on silica gel [8], ammonium persulfate [9], pyridinium chlorochromate under solvent free conditions [10], Magtrievere^{TM}/CrO_2 [11], nitric acid/methylene chloride [12], polymer supported reagents (PVP–N_2O_4 and CrO_3/Dowex 1-X8) [13], among others have been utilized for this reaction. However, these reagents suffer from disadvantages, such as instability, hygroscopicity, toxicity, low selectivity, long reaction times, difficulty of preparation, and a need for a large excess of the reagent. Thus, a mild, more selective, and inexpensive reagent is still in demand.

Since oxygen is highly soluble in subcritical water, it is one of the most attractive oxidants [14]. The increasing environmental concern surrounding the use of toxic and dangerous oxidants has impelled organic chemists to develop oxidation

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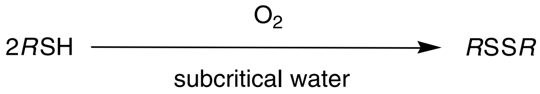
methodologies using molecular oxygen. Molecular oxygen has been known as a reagent for the oxidation of thiols in the presence of different catalysts, such as molecular bromine on hydrated silica gel [15], Ti(IV) in the presence of NaI [16], CsF-celite, and Mn(II) [17] and Co(II) salts of 4-aminobenzoic acid supported on silica gel [18]. In our previous study, we have reported the oxidation of toluenes to aromatic aldehydes with molecular oxygen in subcritical water [19]. In continuation of our recent work an oxidative coupling of thiols with 3-carboxypyridinium trichloroacetatochromate [20], we now wish to report an alternative procedure for this transformation.

Results and Discussions

In the present work, molecular oxygen is used to oxidize thiols to their corresponding disulfides in subcritical water. The dramatic decrease in solvent viscosity and



$$2RSH \xrightarrow[\text{subcritical water}]{O_2} RSSR$$

Scheme 1

Table 1. Oxidation of thiols to disulfides with molecular oxygen in subcritical water

					P_{O_2}/bar[a]			
				A[c]	5	10	15	20
Entry	Substrate	Product[d]	Mp/°C Ref.		Yield/%[b]			
1	$CH_3(CH_2)_3SH$	$CH_3(CH_2)_3$–S–S–$(CH_2)_3CH_3$	Oil [22]	70	75	83	90	95
2	$CH_3(CH_2)_7$–SH	$CH_3(CH_2)_7$–S–S–$(CH_2)_7$–CH_3	Oil [23]	75	80	83	92	95
3	HO–CH_2–CH_2–SH	HO–CH_2–CH_2–S–S–CH_2–CH_2–OH	Oil [23]	80	85	90	92	92
4	$HS(CH_2)_2COOH$	$HOOC(CH_2)_2$–S–S–$(CH_2)_2COOH$	Oil [10]	80	85	93	95	95
5	Cyclohexyl-SH	Cyclohexyl–S–S–cyclohexyl	Oil [24]	70	75	83	90	95
6	*Ph*–SH	*Ph*–S–S–*Ph*	59–61 (61) [22]	85	92	95	95	95
7	*Ph*CH_2SH	*Ph*CH_2–S–S–CH_2*Ph*	70–71 (66–68) [25]	70	75	80	85	95
8	4-CH_3–*Ph*–CH_2SH	4-CH_3–*Ph*–CH_2–S–S–CH_2–*Ph*–CH_3-4	40–42 (40–41) [22]	80	90	95	95	95
9	4-Cl–*Ph*–CH_2SH	4-Cl–*Ph*–CH_2–S–S–CH_2–*Ph*–Cl-4	70–72 (72–74) [26]	82	90	90	95	95
10	2-Pyridyl-SH	2-Phridyl–S–S–pyridyl-2	56–57 (57) [27]	85	92	95	95	95
11	Benzthiazolyl-2-SH	Benzthiazolyl-2-S–S-2-benzthiazolyl	183–185 (183–185) [25]	83	90	92	95	95

[a] Double equivalents of molecular oxygen, 5 bar, 4.63×10^{-3} mol dm^{-3}; 10 bar, 9.26×10^{-3} mol dm^{-3}; 15 bar, 1.38×10^{-2} mol dm^{-3}; 20 bar, 1.85×10^{-2} mol dm^{-3}; [b] relative yield based on quantitative analysis; [c] A: dissolved oxygen in water at atmospheric pressure 1.26×10^{-3} mol dm^{-3}; [d] all products were characterized by IR and ^{1}H NMR and their physical data compared with literature data; reactions conditions: total pressure 40 bar, temperature 100°C

an increase in substrate solubility suggest that subcritical water may be useful as a replacement for environmentally unacceptable solvents for a number of organic reactions [21]. The oxidation of thiols to disulfides in subcritical water were carried out as isothermal experiments at 100°C using different amounts of oxygen (Scheme 1). As shown in Table 1, all thiols converted to the corresponding disulfides, which were isolated in excellent yields. Because aliphatic and aromatic thiols were oxidized to disulfides in the absence of an organic solvent and metal salts/complexes, our method is indeed very green chemistry.

The amount of dissolved oxygen in water at atmospheric pressure was determined according to *Henry*'s law [28] (at 25°C the solubility of O_2 is of $1.296 \cdot 10^{-3}$ mol/kg H_2O). This value was used initially as shown in the Table 1 as entry A. The amount of oxygen was regulated by its pressure. All oxidations were performed by adding 280 cm^3 water, one equivalent of substrate, and two equivalents oxygen. Since longer reaction times did not improve the yields, the time was optimized at 2 h for all oxidations. On the other hand, when oxygen pressure was increased, the yields were not increased beyond 20 bar; an increase in the amount of oxygen led to decomposition of the starting materials converting them into tars. All products were characterized by their spectral data and comparison with reported data. The high-pressure and high-temperature system was used in all reactions.

In conclusion, we developed a practical procedure for the oxidation of thiols to their corresponding disulfides in subcritical water with molecular oxygen in the absence of metal catalysts.

Experimental

Mps were determined on an Electrothermal 9100® apparatus. IR spectra were recorded on a Win First Satellite® model spectrophotometer. ^1H NMR spectra were obtained using a 400 MHz Bruker DPX® instrument.

General Procedure

Oxidations were caried out at 100°C in a stainless steel pressure reactor equipped with N_2 and O_2 inlet, pressure gauge, safety valve, digital temperature reader, heater, and magnetic stirrer. The total pressure was kept at 40 bar by N_2. A glass vessel was inserted into the reactor to avoid the catalytic effect of steel and corossion. The reactor was charged with thiol and 280 cm^3 H_2O. All the valves of the reactor were tightly closed during preheating. N_2 was supplied through a tube into the liquid phase directly. Then the desired oxygen pressure was applied to the vessel through a stainless steel tube into the liquid phase directly, and the total reaction time was 2 h. After the reaction was completed, the reactor was cooled to room temperature and the reaction mixture was extracted with ether ($3 \times 15\,cm^3$). The combined organic layer was dried ($MgSO_4$) and evaporated on a rotary evaporator under reduced pressure. Then the product was chromatographed over silica gel using ethyl acetate/*n*-hexane (1/4) as eluent. Evaporation of the solvent gave fairly pure solids, which were crystallized; the melting point of solid compounds was checked and the solids and oils were identified by IR and ^1H NMR.

Acknowledgement

We are greatful to Mersin University Research Council and TUBITAK (The Scientific and Technical Council of Turkey) for supporting this work (Grant No: TBAG-2235).

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