Catalysis Letters Vol. 111, Nos. 3–4, November 2006 (© 2006)
DOI: 10.1007/s10562-006-0141-8

Mild and highly efficient transformation of thiols to symmetrical disulfides using urea–hydrogen peroxide catalyzed by a Mn(III)–salen complex

Farideh Hosseinpoor and Hamid Golchoubian*

Department of Chemistry, University of Mazandaran, P.O. Box 453, Babolsar, Iran

Received 30 April 2006; accepted 6 May 2006

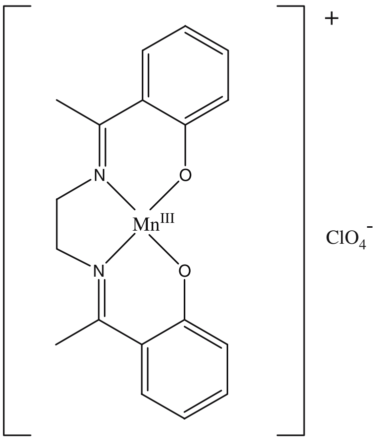
The oxidative coupling of aromatic thiols into the corresponding disulfides with urea–hydrogen peroxide using a Mn(III)–salen complex as catalyst under mild conditions is described. This system provides an efficient, convenient and practical method for the syntheses of symmetrical disulfides.

KEY WORDS: thiols; oxidation; urea–hydrogen peroxide; catalyst; selective oxidation; Mn(III)–salen complex; disulfides.

1. Introduction

Disulfides are of interest compounds in organic synthesis [1–6] and play significant roles in biological [7] and chemical processes [8–9]. Being readily available form commercial suppliers and easily synthesized, thiols serve as the most frequently employed precursors to disulfides. Because disulfides are relatively more stable to organic reaction such as oxidation, alkylation and acylation compared to the corresponding free thiols, the thiol group can conveniently be protected as a disulfide. The desired thiols then can be regenerated from the disulfide either by reduction or by other sulfur–sulfur bond cleavage reaction such as CN^-, OH^- or hydrazines [10]. Thiols can be easily over-oxidized, and therefore, several selective methods of converting thiols into disulfides have been developed e.g. iodine/hydrogen iodide [11], bromine [12], potassium dichromate [13], potassium permanganate/copper(II) sulfate [14], hydrogen peroxide in trifluoroethanol [15] and dimethyl sulfoxide [16–18]. Enzymatic [19] and electrochemical [20] methods are also known to perform this oxidative transformation. Nevertheless, most if not all of reported methods produce the desired disulfides with concomitant formation of solid waste by-products requiring time and solvent consuming purification procedures prior to isolation of the pure product. Additional disadvantages include the use of often expensive, rare or toxic reagents and low yields, long reaction time and high reaction temperature. Thus, there still exists a need for simple, mild, clean and efficient oxidative methods that would produce the target disulfides in high yields without complicated work-up procedures.

In continuation of our current studies in the selective oxidation of hydrocarbons [21, 22] we wish to report a very efficient and simple method for oxidative coupling of alkyl or aryl thiols into the corresponding disulfides using urea–hydrogen peroxide (UHP) catalyzed by the Mn(III) Schiff-base complex 1 under mild conditions as shown in Scheme 1.



Compound 1.

Urea–hydrogen peroxide has many advantages e.g. odorless solid, safe, non-toxic, easy to use and releases hydrogen peroxide locally and more importantly water is the only expected by product.

---

*To whom correspondence should be addressed.
E-mail: h.golchobian@umz.ac.ir

$$2RSH + H_2O_2\ (UHP) \xrightarrow[\text{MeOH, 0 °C, 5-30 min}]{\text{Mn(III) Schiff-base}} RSSR + 2H_2O$$

Scheme 1.

2. Experimental

The complex **1** was prepared by a procedure similar to that used by Karmaker *et al.* [23] However, 1,2-diaminoethane was used instead of 1,3-diaminopropane.

A typical experimental procedure was as follows: to the Mn(III) complex (0.06 mmol) in methanol (2 ml) was added the substrate thiol (1 mmol) and urea–hydrogen peroxide (1 mmol). The reaction mixture was stirred at 0 °C until TLC indicated the reaction was complete. The solvent was then removed and the resulted residue was then washed with a minimal volume of chloroform/n-hexane (1:9 respectively). A simple filtration followed by removal of the solvent from the filtrate gave the product of acceptable purity.

Table 1
Effect of solvent in oxidation coupling of thiols[a]

Entry	Solvent	Time (min)	Conversion (%)[b]
1	MeOH	10	100
2	CH_3CN	120	< 20
3	AcOEt	120	< 5
4	CH_2Cl_2	120	< 5
5	C_6H_6	60	< 5
6	CH_3NO_2	60	< 10
7	DMF	40	100

[a] The reactions were carried out with 1 mmol of *p*-$(CH_3)C_6H_4SH$ at 0 °C with 0.06 mmol of Mn(III) catalyst **1** in 2 ml of solvent and 1 mmol of UHP.
[b] Isolated yield.

Table 2
Oxidative coupling of thiols to disulfides[a]

Entry	Complex **1** (mmol)	UHP (mmol)	Temperature (°C)	Time (min)	Conversion (%)
1	0.06	1.0	0	10	100
2	0.06	1.0	16	15	100
3	0.06	1.0	25	30	75
4	0.06	1.0	70 [b]	20	55
5	0.02	1.0	0	30	100
6	0.04	1.0	0	15	100
7 [d]	–	1.0	0	180	NR [e]
8	0.06	2.0	0	10	100
9[f]	0.06	1.0	0	15	100
10[g]	0.06	1.0	0	45	100
11[h]	0.06	1.0	0	120	100
12[i]	0.06	1.0	0	310	100

[a] Substrate (1 mmol), Mn(III) catalyst **1** (0.06 mmol) and UHP (1 mmol) were stirred at 0 °C in methanol.
[b] The reaction carried out at refluxed temperature.
[c] The selectivity is also reduced to 60%.
[d] The reaction was carried out with 0.06 mmol of Mn(III) acetate in place of complex **1**.
[e] NR: reaction did not occur.
[f] The reaction was carried out with the first recycled complex **1**. The yield was 97%.
[g] The reaction was carried out with the second recycled complex **1**. The yield was 97%.
[h] The reaction was carried out with the third recycled complex **1**. The yield was 97%.
[i] The reaction was carried out with the fourth recycled complex **1**. The yield was 97%.

3. Results and discussion

4-methylthiophenol was selected as a model substrate for optimization of the process. We first examined various solvents to facilitate this transformation and determined that methanol showed the highest yield (Table 1). Furthermore, the reaction was carried out at higher temperature under the same conditions in which, the conversion decreased significantly at elevated temperature (Table 2, entries 1–4). The reason for this result could be due to decomposition of hydrogen peroxide to molecular oxygen and water in presence of Mn(III) complex at elevated temperature. Further, when the oxidative coupling of 4-methylthiophenol was carried out using less catalyst **1**, the reaction was found to reach

Table 3
Oxidative coupling of thiols to disulfides with UHP catalyzed by complex **1**[a]

Entry	Substrate	Time (min)	Yield (%)[b]
1	*p*-$(CH_3)C_6H_4SH$	10	97
2	*p*-BrC_6H_4SH	6	97
3	*p*-ClC_6H_4SH	12	93
4	C_6H_5SH	5	92
5	*p*-FC_6H_4SH	4	90
6	*p*-$(CH_3S)C_6H_4SH$	< 1	90
7	Naphtalenethiol	5	91
8	*o*-OHC_6H_4SH	30	92

[a] The reactions were carried out with 1 mmol of substrate in 2 ml of methanol at 0 °C with 0.06 mmol of Mn(III) catalyst **1** and 1 mmol of UHP.
[b] Isolated yields.

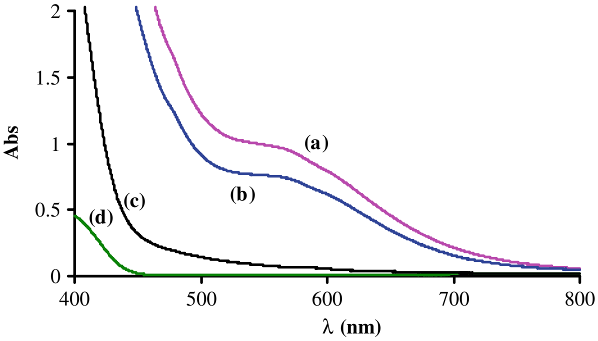


Figure 1. Absorption spectra of (a) the Mn(III) complex **1** in presence of UHP; (b) the Mn(III) complex **1** after the reaction was complete; (c) the Mn(III) complex **1** in presence of thiol; (d) the Mn(II) complex in solvent of methanol.

completion but over a much longer time (Table 2, entries 5 and 6). When other Mn(III) salts were used, such as Mn(III) acetate as catalyst in place of complex **1**, no reaction took place and the starting material was recovered (Table 2, entry 7).

The oxidative coupling of other thiols were then examined using the optimized reaction conditions and oxidation performed almost in excellent yields during 1–30 min (Table 3)

When a methanolic solution of Mn(III)–salen complex in UHP was treated with substrate the initial dark-brown color faded to a yellow solution with disappearance of the broad band at about 550 nm. Upon the completion of reaction, the original dark-brown color appeared again within 5 min. Performing the same experiment in the absence of UHP, the color fading was observed again which was darken upon addition of UHP (Figure 1). These spectral changes are attributed to the formation of a Mn(II)–salen intermediate which are generated by one-electron reduction from thiolate anions and formation of sulfur radicals. Coupling of the radicals turns out the disulfide product. Then Mn(II)–salen is oxidized to its $\mathrm{Mn^{III}}$ counterpart by UHP and the catalyst **1** is regenerated. Interestingly, increase the concentration of UHP dose not effect the rate of the reaction (Table 2 entry 8). This might imply that the reaction 2 in Scheme 1 is the slowest step in the oxidation processes.

Furthermore, when acrylonitrile was added to the reaction mixture under argon atmosphere, turbidity appeared indicating the involvement of free radicals in the reaction [24]. Basing on the experimental results the proposed mechanism for the oxidation of thiols by UHP under Mn(III) catalyst can be as summarized in Scheme 2.

$$\text{(1)}\quad \mathrm{RSH} \longrightarrow \mathrm{RS^-} + \mathrm{H^+}$$

$$\text{(2)}\quad \mathrm{Mn^{III}} + \mathrm{RS^-} \longrightarrow \mathrm{Mn^{II}} + \mathrm{RS^{\bullet}}$$

$$\text{(3)}\quad 2\mathrm{RS^{\bullet}} \longrightarrow \mathrm{RSSR}$$

$$\text{(4)}\quad \mathrm{Mn^{II}} + \mathrm{H_2O_2} + 2\mathrm{H^+} \longrightarrow \mathrm{Mn^{III}} + 2\mathrm{H_2O}$$

Scheme 2.

The reusability of the catalyst was monitored using sequential oxidation of p-$(\mathrm{CH_3})\mathrm{C_6H_4SH}$ with UHP. For each of repeated reactions and isolation of product, the resulted residue was treated with water. Evaporation of the aqueous layer afforded the manganese salt **1**, which was consecutively reused four times without loss of its activity (Table 2, entries 9–12).

Multi scale oxidation of p-$(\mathrm{CH_3})\mathrm{C_6H_4SH}$ (2000 mmol) was also investigated. The results demonstrate that oxidation took place in good yield (typically less than 2% yield is lost).

Catalyst stability has been followed by IR and UV–Vis spectroscopies. The results indicated that the catalyst being used after four times showed no detectable change in its IR and UV–Vis spectra.

4. Conclusion

In summary, the results indicate the complex **1** is an efficient catalyst in the oxidation of thiol into disulfide by UHP as oxidizing reagent. Although the exact mechanism of this transformation is still unclear, the catalytic system was carried out via the formation of Mn(II)–salen complex. Moreover, this catalytic oxidation system takes on the clean, safety and operationally simple characteristic, and the yields of the products are high, so the oxidation method meets the needs of contemporary green chemistry and is suitable for practical synthesis.

Acknowledgment

We are grateful for the financial support of Mazandaran University of the Islamic Republic of Iran.

References

[1] S. Oae, *Organic Sulfur Chemistry: Structure and Mechanism* (CRC Press, Boca Raton, FL, 1991).

[2] R.J. Cremlyn, *An Introduction to Organosulfur Chemistry* (Wiley & Sons, New York, 1996).

[3] G. Ledung, M. Bergkvist, A.P. Quist, U. Gelius, J. Carlsson and S. Oscarsson, Langmuir 17 (2001) 6056.

[4] Y. Nishiyama, K. Maehira, J. Nakase and N. Sonoda, Tetrahedron Lett. 46 (2005) 7415.

[5] J. Langer, R. Fischer, H. Gorls and D.J. Walther, Organomet.Chem. 689 (2004) 2952.

[6] E. Zysman-Colman and D.N. Harpp, J. Org. Chem 70 (2005) 5964.

[7] Langer, R. Fischer, H. Gorls, D. Walther, Am. J. Physiol. Renal Physiol. 278 (2000) 2952.

[8] D.C. Jocelyn, *Biochemistry of the Thiol Groups* (Academic press, New York, 1992).

[9] R.J. Cremlyn, *An Introduction to Organosulfur Chemistry* (Wiley and Sons, New York, 1996).

[10] S.N. Maiti, P. Spevak, M.P. Singh and R.G. Micetich, Synth. Commun. 18 (1988) 575.

[11] R.F. Lang, T.D Ju, G. Kiss, C.D. Hoff, J.C. Bryan and G.J. Kubas, Inorg. Chim. Acta 259 (1997) 317.

[12] M.H. Ali and M. McDermott, Tetrahedron Lett. 43 (2002) 6271.

[13] S. Patel and B.K. Mishra, Tetrahedron Lett. 45 (2004) 32.

[14] A. Shaabani and D.J. Lee, Tetrahedron Lett. 42 (2001) 5833.

[15] V. Kesavan, D. Bonnet-Delpon, J.-P. Begue, Synthesis (2000) 223.

[16] S.T.A. Shad, K.M. Khan, M. Fecker and W. Voelter, Tetrahedron Lett 44 (2003) 6789.

[17] R. Sanz, R. Aguado, M.R. Pedrosa, F.J. Arnaiz, Synthesis (2002) 856.

[18] B. Karimi, H. Hazatkhani, D. Zareyee, Synthesis (2002) 2513.

[19] M. Sridhar, S.K. Vadivel and U.T. Bhalerao, Synth. Commun. 28 (1998) 1499.

[20] S.L.S. Leite, V.L. Pardini and H. Viertler, Synth. Commun. 20 (1990) 393.

[21] H. Golchoubian and A. Nemati Kharat, Polish J. Chem. 79 (2005) 825.

[22] H.R. Mardani and H. Golchoubian, Tetrahedron Lett. 47 (2006) 2349.

[23] R. Karmaker, C.R. Choudhury, G. Bravic, J.-P. Sutter, S. Mitra Polyherdon 23 (2004) 949.

[24] A. Palaniappan, S. Srinivasan and S. Senthilkumar, Oxid. Commun. 27 (2004) 635.