May 2004 Notes Chem. Pharm. Bull. 52(5) 625—627 (2004)

# Aerobic Oxidation of Thiols to Disulfides Catalyzed by Trichlorooxyvanadium

Masayuki KIRIHARA,[*,a] Kumiko OKUBO,[a] Tomoyuki UCHIYAMA,[a] Yoko KATO,[a] Yuta OCHIAI,[b]
Shinya MATSUSHITA,[a] Akihiko HATANO,[a] and Kan KANAMORI[c]

[a] *Department of Materials Science, Shizuoka Institute of Science and Technology; 2200–2 Toyosawa, Fukuroi, Shizuoka 437–8555, Japan:* [b] *Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University; 2630 Sugitani, Toyama 930–0194, Japan: and* [c] *Faculty of Science, Department of Chemistry, Toyama University; 3190 Gofuku, Toyama 930–8555, Japan.* Received December 16, 2003; accepted February 9, 2004

**Thiols were converted into disulfide by the aerobic oxidation catalyzed by trichlorooxyvanadium in the presence of molecular sieves 3A.**

**Key words** thiol; disulfide; oxidative coupling; aerobic oxidation

Oxidative coupling of thiols to disulfides is of interest from both a synthetic and a biological point of view, because disulfides are useful reagent in organic synthesis[1—3] and essential moieties of biologically active compounds for peptide and protein stabilization.[4] Thiols can be easily over-oxidized, and therefore, several selective methods of converting thiols into disulfides have been developed. For example, iodine/hydrogen iodide,[5] bromine,[6,7] potassium permanganate/copper(II) sulfate,[8] hydrogen peroxide in trifluoroethanol,[9] and dimethyl sulfoxide[10—12] are used for this purpose. Most of the existing methods suffer from drawbacks such as the use of stoichiometric amounts of reagents that generate undesirable waste materials. To overcome these drawbacks, catalytic oxidation using oxygen as a co-oxidant has been developed by several groups.[13—18]

We have been investigating the aerobic oxidation of organic compounds catalyzed by higher valent vanadium compounds.[19—36] Stoichiometric higher valent vanadium compounds are known to oxidize thiols to produce disulfides,[37,38] and a catalytic amount of vanadyl acetylacetonate is also known to cause the oxidative coupling of thiols in the presence of *t*-butylhydroperoxide.[39] However, there have been no reports about the aerobic oxidative coupling of thiols catalyzed by vanadium compounds. We now describe a novel aerobic oxidative coupling of thiols to disulfides using trichlorooxyvanadium ($VOCl_3$) as a catalyst (Chart 1).

We first examined the oxidation of didodecylthiol as a model substrate with 0.4 eq of $VOCl_3$ under an oxygen atmosphere in several kinds of solvents (Table 1). The reaction efficiently proceeded in aprotic polar solvents such as ethyl acetate (run 3) and acetonitrile to provide didodecyl disulfide[40] (run 4).

We then investigated the reaction of butanthiol with several higher valent vanadium catalysts in ethyl acetate under an oxygen atmosphere (Table 2). Dibutyl disulfide[41] was quantitatively obtained in the case of $VOCl_3$ (a pentavalent vanadium) (run 1). On the other hand, tetravalent vanadiums {vanadyl chloride ($VOCl_2$) (run 2) and vanadyl acetylacetonate [$VO(acac)_2$] (run 3)} did not have sufficient catalytic activity.

Although the oxidation of butanthiol smoothly proceeded to afford the disulfide, over 0.4 eq of $VOCl_3$ was required to complete the reaction (Table 3).

$$\text{R—SH} \xrightarrow{\text{cat. } VOCl_3,\ O_2} \text{1/2 RS—SR}$$

Chart 1

Table 1

$$CH_3(CH_2)_{11}\text{–SH} \xrightarrow[\text{1/2 } CH_3(CH_2)_{11}S\text{–}S(CH_2)_{11}CH_3]{0.4\text{ eq } VOCl_3,\ O_2,\ \text{solvent}}$$

| Run | Solvent | Time | Yield |
|---|---|---|---|
| 1 | $C_6H_6$ | 5 d | 52% |
| 2 | $CH_2Cl_2$ | 44 h | 51% |
| 3 | AcOEt | 22 h | 93% |
| 4 | $CH_3CN$ | 26 h | 82% |
| 5 | $CH_3OH$ | 51 h | Trace |

Table 2

$$n\text{-Bu–SH} \xrightarrow[\text{AcOEt}]{0.4\text{ eq catalyst, } O_2} \text{1/2 } n\text{-BuS–S}n\text{-Bu}$$

| Run | Catalyst | Time | Yield |
|---|---|---|---|
| 1 | $VOCl_3$ | 3 h | Quant |
| 2 | $VOCl_2$ | 41 h | 13% |
| 3 | $VO(acac)_2$ | 41 h | 28% |

Table 3

$$n\text{-Bu–SH} \xrightarrow{\text{catalyst, } O_2,\ \text{AcOEt}} \text{1/2 } n\text{-BuS–S}n\text{-Bu}$$

| Run | Catalyst | Time | Yield |
|---|---|---|---|
| 1 | 0.4 eq $VOCl_3$ | 3 h | Quant |
| 2 | 0.3 eq $VOCl_3$ | 28 h | 66% |
| 3 | 0.2 eq $VOCl_3$ | 24 h | 30% |

We assumed that water produced from the oxidative coupling of a thiol deactivated the vanadium catalyst. Therefore, molecular sieves 3A were added to the reaction mixture to remove the water.[42,43] In the presence of the molecular sieves 3A, only 0.05 eq $VOCl_3$ was enough to complete the reaction (Chart 2).

---

[*] To whom correspondence should be addressed. e-mail: kirihara@ms.sist.ac.jp

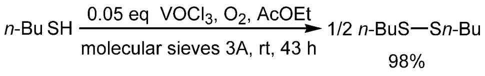
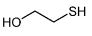
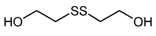
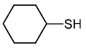
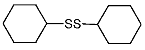
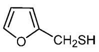
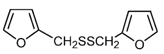
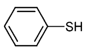
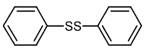
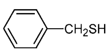
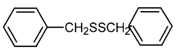
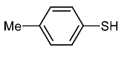
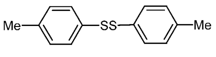
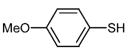
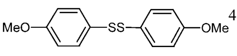


Chart 2

Table 4

$$\mathrm{RSH} \xrightarrow[\text{molecular sieves 3A, rt}]{0.05\,\text{eq VOCl}_3,\ \text{O}_2,\ \text{AcOEt}} 1/2\ \text{RS–SR}$$

| Entry | Thiol | Product[a] | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | $CH_3(CH_2)_{11}SH$ | $CH_3(CH_2)_{11}SS(CH_2)_{11}CH_3$ [40] | 111<br>(22)[b] | 88<br>(93)[b] |
| 2 | $CH_3(CH_2)_3SH$ | $CH_3(CH_2)_3SS(CH_2)_3CH_3$ [41] | 43<br>(3)[b] | 98<br>(quant)[b] |
| 3 |  |  [44] | 1.5<br>(0.5)[b] | 84<br>(75)[b] |
| 4 |  |  [13] | 41<br>(5)[b] | 53[c]<br>(93)[b] |
| 5 |  |  [45] | 109 | 80 |
| 6 |  |  [13] | 52<br>(22)[b] | 93<br>(99)[b] |
| 7 |  |  [16] | 74<br>(4)[b] | 91<br>(99)[b] |
| 8 |  |  [46] | 20 | 96 |
| 9 |  |  [46] | 66 | 98 |

*a*) The physical data of the products were consistent with those of references. *b*) 0.4 eq of $VOCl_3$ was used without molecular sieves 3A. *c*) Unidentified by-products were obtained.

This method is equally applicable for the oxidative coupling of several kinds of thiols (Table 4). In the parentheses, we also show the results of the reaction using 0.4 eq $VOCl_3$ without molecular sieves. Although the reaction rates were relatively slow, dislufides were efficiently obtained in most cases. As noted in the entry 3, 2-mercaptoethanol was oxidized much faster than in the other cases. The reason for this interesting phenomenon has not been clarified.

In conclusion, the $VOCl_3$-catalyzed aerobic oxidative coupling of thiols should be a good method to prepare disulfides.

## Experimental

**General Procedures** Thiols and vanadium compounds were obtained from Wako Pure Chemical Industries, Kanto Kagaku, Nacalai Tesque, or Tokyo Kasei Kogyo without purification. Products were characterized by comparison of their physical data with those of known samples.

**The Aerobic Oxidation of Thiols Catalyzed by Trichlorooxyvanadium in the Presence of Molecular Sieves 3A: General Procedures** To a stirred mixture of thiol (4.0 mmol), molecular sieves 3A (1.0 g) and ethyl acetate (4.0 ml) was added $VOCl_3$ (35 mg, 0.2 mmol) under an oxygen atmosphere at room temperature. The reaction was monitored by thin layer chromatography and was continuously stirrered under the same conditions until the thiol disappeared. After the reaction was completed, a drop of saturated aqueous sodium bicarbonate was added and diluted with ethyl acetate (30 ml). The resulting mixture was filtered with Cerite and the filtrate was dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane–ethyl acetate as the eluents) to afford the pure products.

**Acknowledgments** This work was supported in part by the Regional Science Promotion Program of Japan Science and Technology Corporation. We would like to express our appreciation to Mr. Masao Yaso (Regional Science Promotion Program of Japan Science and Technology Corporation), for his helpful suggestions.

## References

1) For example, see: Ogawa A., Nishiyama Y., Kambe N., Murai S., Sonoda N., *Tetrahedron Lett.*, **28**, 3271—3274 (1987).
2) For example, see: Antebi S., Alper H., *Tetrahedron Lett.*, **26**, 2609—2612 (1985).
3) For example, see: Bischoff L., David C., Martin L., Meudal H., Roques B.-P., Fournié-Zaluski M.-C., *J. Org. Chem.*, **62**, 4848—4850 (1997).
4) Bodanszky M., "Principles of Peptide Synthesis: Reactivity and Structure Concepts in Organic Chemistry," Springer Verlag, Hiderberg, 1984, p. 307.
5) Aida T., Akasaka T., Furukawa N., Oae S., *Bull. Chem. Soc. Jpn.*, **49**, 1441—1442 (1976).
6) Wu X., Reike R. D., Zhu L., *Synth. Commun.*, **26**, 191—196 (1996).
7) Drabowicz J., Mikolajczyk M., *Synthesis*, **1980**, 32—34 (1980).
8) Noureldin N. A., Caldwell M., Hendry J., Lee D. G., *Synthesis*, **1998**, 1587—1589 (1998).
9) Kesavan V., Bonnet-Delpon D., Bégué J.-P., *Synthesis*, **2000**, 223—225 (2000).
10) Tam J. P., Wu C.-R., Liu W., Zhang J.-W., *J. Am. Chem. Soc.*, **113**, 6657—6662 (1991).
11) Sanz R., Aguado R., Pedrosa M. R., Arnáiz F. J., *Synthesis*, **2002**, 856—858 (2002).
12) Karimi B., Hazarkhani H., Zareyee D., *Synthesis*, **2002**, 2513—2516 (2002).
13) For example: Liu K.-T., Tong Y.-C., *Synthesis*, **1978**, 669—670 (1978).
14) For example: Simándi L. I., Németh S., Rumelis N., *J. Mol. Catal.*, **42**, 357—360 (1987).
15) For example: Cervilla A., Corma A., Fornes V., Llopis E., Palanca P., Rey F., Ribera A., *J. Am. Chem. Soc.*, **116**, 1595—1596 (1994).
16) For example: Iranpoor N., Zeynizadeh B., *Synthesis*, **1999**, 49—50 (1999).
17) For example: Rao T. V., Rao K. N., Jain S. L., Sain B., *Synth. Commun.*, **32**, 1151—1157 (2002).
18) For example: Shah S. T. A., Khan K. M., Fecker M., Voelter W., *Tetrahedron Lett.*, **44**, 6789—6791 (2003).
19) For example: Kirihara M., Takizawa S., Momose T., *J. Chem. Soc. Perkin Trans. 1*, **1998**, 7—8 (1998).
20) For example: Kirihara M., Ichinose M., Takizawa S., Momose T., *Chem. Commun.*, **1998**, 1691—1692 (1998).
21) For example: Kirihara M., Ochiai Y., Takizawa S., Takahata H., Nemoto H., *Chem. Commun.*, **1999**, 1387—1388 (1999).
22) For example: Kirihara M., Ochiai Y., Arai N., Takizawa S., Momose T., Nemoto H., *Tetrahedron Lett.*, **40**, 9055—9057 (1999).
23) Organic syntheses using vanadium reagents developed by other groups: Hirao T., *Chem. Rev.*, **97**, 2707—2724 (1997).
24) Organic syntheses using vanadium reagents developed by other groups: Takada T., Sakurai H., Hirao T., *J. Org. Chem.*, **66**, 300—302 (2001).
25) Organic syntheses using vanadium reagents developed by other groups: Hirao T., Morimoto C., Takada T., Sakurai H., *Tetrahedron Lett.*, **42**, 1961—1963 (2001).
26) Organic syntheses using vanadium reagents developed by other groups: Hirao T., Morimoto C., Takada T., Sakurai H., *Tetrahedron*, **57**, 5073—5079 (2001).
27) Organic syntheses using vanadium reagents developed by other groups: Hirao T., Takada T., Sakurai H., *Org. Lett.*, **2**, 3659—3661 (2000).
28) Organic syntheses using vanadium reagents developed by other groups: Ishikawa T., Nonaka S., Ogawa A., Hirao T., *Chem. Commun.*, **1998**, 1209—1210 (1998).
29) Organic syntheses using vanadium reagents developed by other groups: Ishikawa T., Ogawa A., Hirao T., *J. Am. Chem. Soc.*, **120**, 5124—5125 (1998).
30) Organic syntheses using vanadium reagents developed by other groups: Ishikawa T., Ogawa A., Hirao T., *Organometallics*, **17**, 5713—5716 (1998).
31) Organic syntheses using vanadium reagents developed by other groups: Hirao T., Asahara M., Muguruma Y., Ogawa A., *J. Org. Chem.*, **63**, 2812—2813 (1998).

32) Organic syntheses using vanadium reagents developed by other groups: Hirao T., *J. Inorg. Biochem.*, **80**, 27—33 (2000).

33) Organic syntheses using vanadium reagents developed by other groups: Hoshino Y., Yamamoto H., *J. Am. Chem. Soc.*, **122**, 10452—10453 (2000).

34) Organic syntheses using vanadium reagents developed by other groups: Bolm C., Küehn T., *Synlett*, **2000**, 899—901 (2000).

35) Organic syntheses using vanadium reagents developed by other groups: Chien C.-T., Kuo J.-H, Li C.-H., Barhate N. B., Hon S.-W., Li T.-W., Chao S.-D., Liu C.-C., Li Y.-C., Chang I.-H., Lin J.-S., Liu C.-J., Chou Y.-C., *Org. Lett.*, **3**, 3729—3732 (2001).

36) Organic syntheses using vanadium reagents developed by other groups: Hwang D.-R., Chen C.-P., Uang B.-J., *Chem. Commun.*, **1999**, 1207—1208 (1999).

37) Hill J., McAuley A., *J. Chem. Soc. A*, **1968**, 2405—2408 (1968).

38) Pickering W. F., McAuley A., *J. Chem. Soc. A*, **1968**, 1173—1176 (1968).

39) Raghavan S., Rajender A., Joseph S. C., Rasheed M. A., *Synth. Commun.*, **31**, 1477—1480 (2001).

40) Huang Y., Zhang Y., Wang Y., *Synth. Commun.*, **27**, 1043—1047 (1997).

41) Iranpoor N., Firouzabadi H., Zolfigol M. A., *Synth. Commun.*, **28**, 367—375 (1998).

42) Molecular sieves are used to remove water formed during the vanadium compound-catalyzed aerobic oxidation of propargylic alcohols. See: Maeda Y., Kakiuchi N., Matsumura S., Nishimura T., Uemura S., *Tetrahedron Lett.*, **42**, 8877—8879 (2001).

43) Molecular sieves are used to remove water formed during the vanadium compound-catalyzed aerobic oxidation of propargylic alcohols. See: Maeda Y., Kakiuchi N., Matsumura S., Nishimura T., Kawamura T., Uemura S., *J. Org. Chem.*, **67**, 6718—6724 (2002).

44) Meshram H. M., Bandyopadhyay A., Reddy G. S., Yadav J. S., *Synth. Commun.*, **30**, 701—706 (2000).

45) "Aldrich Handbook of Fine Chemicals 2003—2004," Aldrich Chemical Company, Milwaukee, 2003.

46) Huang X., Chan C.-C., *Synthesis*, **1982**, 1091—1092 (1982).