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Oxidation by Chemical Manganese Dioxide. Part 2.[1] Simple and High-yielding Synthesis of Symmetrical Disulfides *via* the Oxidative Coupling of Thiols†

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Aromatic, aliphatic, and alicyclic thiols readily underwent oxidative coupling with chemical manganese dioxide in hexane to afford the corresponding disulfides in essentially quantitative yields under relatively mild conditions.

Thiols (R—SH, **1**) and disulfides (RS—SR, **2**) occur in nature and the cysteine-cystine interconversion is a well known important biological process in living organisms.[2] Oxidative coupling of **1** to **2** using various laboratory reagents[3] has been achieved very easily under mild conditions even with atmospheric air (plus alumina as the solid base), for example.[4] In view of economical, practical, and recent environmental[5] demands, however, use of expensive or toxic oxidizing reagents, long reaction times, synthetically unsatisfactory yields of **2** and/or production of large volume effluents in the conventional procedures may now make them unattractive.[6]

In the preceding paper,[1] we have reported the facile oxidation of benzylic alcohols with a combination of chemical manganese dioxide (CMD)[7] and molecular sieves (MS) in hexane. Since S—H bonds in **1** are in general weaker than O—H bonds in alcohols,[8] we have tested the synthetic value of the CMD/MS system for the oxidative dimerization of various thiols to the disulfides (Scheme 1).

$$\underset{\mathbf{1}}{2\,\mathrm{R{-}SH}} \xrightarrow[\text{Hexane, reflux}]{\text{CMD, MS}} \underset{\mathbf{2}}{\mathrm{R{-}S{-}S{-}R}}$$

1–2	R	1–2	R	1–2	R
a	Ph	**g**	*o*-ClC_6H_4	**m**	C_8H_{17}
b	*p*-$MeOC_6H_4$	**h**	*m*-ClC_6H_4	**n**	$C_{10}H_{21}$
c	*o*-MeC_6H_4	**i**	*p*-ClC_6H_4	**o**	$C_{12}H_{25}$
d	*m*-MeC_6H_4	**j**	*p*-$O_2NC_6H_4$	**p**	$C_{14}H_{29}$
e	*p*-MeC_6H_4	**k**	$PhCH_2$	**q**	*c*-C_5H_9
f	*p*-BrC_6H_4	**l**	C_6H_{13}	**r**	*c*-C_6H_{11}

Scheme 1

Oxidative coupling of **1** was carried out simply by gently refluxing a heterogeneous mixture of **1**, CMD, and MS in hexane under a dry and inert atmosphere. Stoichiometrically, it is likely that 1 mol of CMD can oxidize 2 mol of **1** to give 1 mol of **2** and 1 mol of water, eqn. (1),

$$2\mathrm{RS{-}H} + \mathrm{Mn^{IV}O_2} \longrightarrow \mathrm{RS{-}SR} + \mathrm{Mn^{II}O} + \mathrm{H_2O} \qquad (1)$$

since the reduction of $Mn^{IV}O_2$ to $Mn^{II}O$ is a two-electron transfer process. The GLC analysis of a test run performed with 1 mmol of benzenethiol **1a** and 0.5 mmol of CMD showed that the reaction was clean and uncomplicated by the formation of by-products, but a considerable amount of **1a** still remained (19%) and diphenyl disulfide **2a** was obtained only in 81% yield even after 3 h. Prolonged reaction (*ca.* 5 h) enabled 100% conversion of **1a** and produced **2a** in 97% yield, but was experimentally unattractive. In contrast, a repeat run with 1 mmol of CMD proceeded smoothly, and **1a** was consumed completely within 1 h, giving quantitative yield of **2a**. Thus, the current procedure can be favorably compared to earlier methods using AMD as reported by Wallace[9a] [89% after 22 h reaction in xylene at 55 °C, [AMD]/[**2a**] = 1 (mole ratio)] and by Papadopoulos *et al.*[9a] [92% after 5–6 h reaction in refluxing $CHCl_3$, [AMD]/[**2a**] = 5 (weight ratio)] in terms of the yield of **2a** and especially of the reaction period. In addition, from economical and environmental points of view, hexane is a more attractive solvent than a halomethane or an aromatic solvent.

The oxidations of the benzenethiol series **1a**–**j** were accomplished readily to give the disulfides **2a**–**j** in nearly quantitative yields, regardless of electronic properties (**1a**, **b**, **e**, **f**, **i**, and **j**) and the positions of substituents on the benzene ring (**1c**–**e** and **1g**–**i**), despite the facts that *o*-substituents exhibited strong steric hindrance in the oxidations of benzylic alcohols with AMD[10] and also with CMD.[1] The CMD/MS system was also useful for the oxidations of the aralkyl thiol **1k**, aliphatic thiols bearing medium to long alkyl chains **1l**–**p**, and alicyclic thiols **1q**, **r**. It should be noted that although the ease with which thiols are oxidized by certain sulfoxides is strongly dependent on the acidities of the thiols, *viz.* **1a** > **1k** ≫ **1o**,[11] there is no significant difference in the reactivities of these thiols under our experimental conditions. In fact, the oxidation of an equimolar mixture of **1a** and **1o** gave **2a** (20% by GLC), **2o** (22%), and the unsymmetrical disulfide, Ph—S—S—$C_{12}H_{25}$ (57%), clearly indicating that **1o** has comparable reactivity to that of **1a** towards CMD.

Summing up, the CMD/MS system in refluxing hexane can be conveniently used for the oxidative coupling of thiols and is applicable to a wide range of substrates.

Experimental

General.—Molecular sieves 4A powder (Aldrich) was predried in an oven (350 °C, 6 h). Thiols **1a**–**r** and CMD (Wako) were used as received. Hexane was rigourously dried, distilled and stored over molecular sieves. Mps were determined on a Yanagimoto MP-S3 melting point apparatus and are uncorrected. Analytical gas chromatography was performed on a Shimadzu GC-4CM instrument with a 2 m × 5 mm diameter glass column packed with 3% OV-17 on Uniport HP and interfaced with a Shimadzu Chromatopac C-R6A integrator, with temperature programming.

Oxidation Procedure.—This was similar to that described previously[1] and the reactions of **1a**–**r** (1 mmol) were carried out with CMD (1–2 mmol), predried MS (0.5 g) and hexane (10 ml), and 100% conversion was attained within 1 h in each experiment. In addition, the successful synthesis of **2a** (98%) on a multigram scale was achieved by using **1a** (40 mmol), CMD (44 mmol) and predried MS (3 g) in hexane (50 ml) from 1 h reaction.

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