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Oxidative coupling of thiols to disulfides using a solid anhydrous potassium phosphate catalyst

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Abstract—Thiols are oxidized to the corresponding disulfides with a mild base, anhydrous potassium phosphate, under ambient conditions in the presence of air.

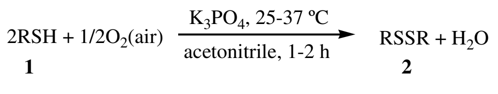
Applications in biochemical and industrial processes render oxidation of thiols to disulfides as an important reaction class.[1] Moreover thiols can be conveniently protected as disulfides and be regenerated by cleavage of the S–S bond.[2] Thus, oxidation of thiols to disulfides is one of the widely studied transformations. Thiols are susceptible to over oxidation and hence there are reports on their controlled oxidation.[3] Oxidative couplings of thiols to disulfides have been reported in the presence of dimethyl sulfoxide,[4] halogens or variants,[5] nitric oxide,[6] sodium perborate,[7] calcium hypochlorite and silica gel,[8] phase transfer catalysts,[9] hydrogen peroxide in fluoro alcohols[10] and even with superoxide ions.[11] Enzymes[12] and electrochemical techniques[13] have also been utilized for this purpose. Nevertheless, it is desirable to achieve this transformation using a clean and effective reagent viz. air or oxygen. Oxidation of thiols depends upon their acidities and hence they can be subjected to base catalysis.[14] Consequently, oxidation of thiols with air or oxygen in the presence of basic alumina,[15] alkali base,[16] CsF-Celite,[17] a weakly basic mineral support[18] and hydrotalcite clay[19] have also been studied. Oxidation of thiols with O_2, catalyzed by Co(II) phthalocyanines has been studied in ionic liquids.[20]

In our laboratory we have studied alkylations of different carbon acids using solid K_3PO_4 as a base.[21] Thus we considered it worthwhile to explore its efficacy in oxidation of thiols to disulfides. K_3PO_4 has also been utilized for reactions such as nitroladol,[22a] Knoevenagel condensation[22b] and dithiocarbamates,[22c] whereas hydrated K_3PO_4 has frequently been used in transition metal catalyzed cross coupling reactions.[22d]

In this communication we report an efficient and simple method for oxidative coupling of alkyl or aryl thiols to the corresponding disulfides in the presence of the weak solid base, potassium phosphate (Scheme 1).

In a typical reaction, a mixture of 1 g (9.1 mmol) of thiophenol, 994 mg (4.55 mmol) anhydrous K_3PO_4 and 20 mL of acetonitrile were stirred at 25 °C in a round bottom flask equipped with an air bubbler. GC analysis of the reaction mixture revealed complete conversion to the disulfide after 1 h of reaction. Similarly other substrates were subjected to the above reaction conditions giving the corresponding disulfides. The results are listed in Table 1.

Our earlier studies established that K_3PO_4[21] was basic enough to deprotonate a substrate with a pK_a as high



$$\underset{\mathbf{1}}{2RSH} + 1/2O_2(\text{air}) \xrightarrow[\text{acetonitrile, 1-2 h}]{K_3PO_4,\ 25\text{-}37\ ^\circ C} \underset{\mathbf{2}}{RSSR} + H_2O$$

Where: R=Ph, 4-ClC_6H_4, 4-*tert*-butyl-C_6H_4, PhCH_2,
cyclohexyl, *n*-C_5H_{11}, 2-pyridyl

Scheme 1.

Keywords: Disulfides; Autoxidation; Mild base.

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Table 1. Oxidative coupling of thiols **1** to the corresponding disulfides **2**[a]

Entry	Reactant	Yield of disulfide (%)[c]
1	Thiophenol	91
2	Benzyl mercaptan	88
3	4-*tert*-Butylbenzenethiol	85
4	4-Chlorobenzenethiol	85
5	Cyclohexanethiol	89
6	Pyridine-2-thiol	92
7	Pentane-1-thiol[b]	89

[a] Reaction conditions: substrate, 1 g; anhydrous K_3PO_4, 50 mol % of the substrate; acetonitrile, 20 mL; air, 25–50 cm^3/min; temp, 25 °C; time, 1–2 h.

[b] Temp, 37 °C; 12 h.

[c] Isolated yield (purity and identity of the products was confirmed by NMR, GC and GC–MS).

as 21, consequently we expected that active substrates such as thiols with pK_a values in the range of 7–11 could be easily converted to their conjugated base in the presence of K_3PO_4 (Table 1). In fact the oxidation reaction was efficient with alkyl, cycloalkyl, aryl and benzyl thiols. Heteroaromatic thiols were also effectively transformed to their corresponding disulfides.

The reusability of K_3PO_4 was verified in a thiophenol oxidation reaction. The amount of base employed was half the mole quantity of the substrate. The base could be reclaimed and reused in a subsequent reaction after filtration and drying.

We propose a reaction mechanism where, in the presence of the phosphate base, a mercaptide anion is generated 1. The latter reacts with oxygen to yield a thiyl radical and peroxide (or superoxide) anion 2. The thiyl radical thus generated dimerizes to give the disulfide 3,[16b] as follows:

$$RSH + K_3PO_4 \rightarrow RS^-K^+ + K_2HPO_4 \qquad (1)$$

$$2RS^-K^+ + O_2 \rightarrow 2RS^\bullet + O_2^{-2} + 2K^+ \qquad (2)$$

$$2RS^\bullet \rightarrow R\text{–}S\text{–}S\text{–}R \qquad (3)$$

$$2K^+ + 2K_2HPO_4 + O_2^{-2} \rightarrow 2K_3PO_4 + H_2O + 0.5O_2 \qquad (4)$$

In view of the complete recovery of potassium phosphate our mechanism evidently differs from previous schemes, where, in the presence of water, peroxide or superoxide anions decompose to produce hydroxide anions and oxygen.[14b,16b] We assume that the superoxide or peroxide anions are quenched giving oxygen and water and regenerating K_3PO_4 (step 4).

To conclude, we have demonstrated the application of anhydrous K_3PO_4 as a catalyst in the facile autoxidation of thiols. Symmetrical disulfides were obtained in high yields and purity under simple and mild reaction conditions.

Procedure for the preparation of diphenyl disulfide: Thiophenol 9.1 mmol (1.0 g), anhydrous 97% K_3PO_4 4.55 mmol (994 mg) and acetonitrile 20 mL were stirred together in a glass reactor equipped with an air purge at 25 °C. Air was purged at a rate of 25–50 cm^3/min. The progress of the reaction was monitored by GC. After completion of the reaction (1 h) the organic layer was decanted, and the solid was washed twice with 10 mL of acetonitrile and filtered. The combined organic layer was concentrated under reduced pressure to give a solid, then dried under vacuum. The weight of diphenyl disulfide was 904 mg (91% of theoretical yield). The identity of the product was confirmed by GC–MS and NMR analysis.

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