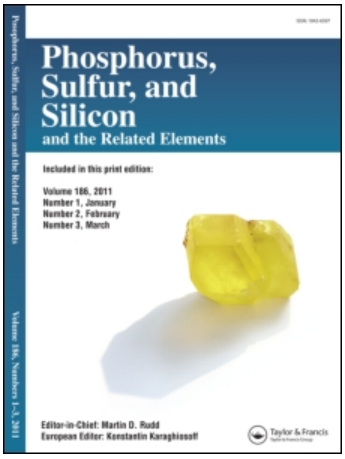

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Thiols are oxidized to the corresponding disulfides using K^+ / CH_3CN system under ambient conditions in the presence of air. This system provides a convenient, rapid, and efficient aerobic oxidative for the syntheses of symmetrical disulfides.

Keywords Aerobic oxidative; disulfide; K^+/CH_3CN; thiol

INTRODUCTION

Transformation of thiols to disulfides is important from both synthetic and biochemical points of view.[1–3] Disulfides have found industrial applications as vulcanizing agents,[4] flavours,[5,6] and drugs.[7] They are also important synthetic intermediates with many applications in organic synthesis.[8] Recently, they have been frequently used in dynamic combinatorial synthesis.[9–12] Many procedures and methods have been devised for this transformation.[13–31] However, there is still an interest in developing a clean, mild and efficient oxidative methods that would produce the target disulfides in high yields without complicated work-up procedures.

Generally molecular oxygen is considered as an ideal "green" oxidant due to its strength and lack of toxic byproducts. Consequently, oxidation of thiols with air or oxygen in the presence of basic alumina,[32]

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CsF-Celite,[33] rhodium complex,[34] anhydrous potassium phosphate[35] and a manganese(III) Schiff-base complex[36] have also been studied.

In our laboratory, we have prepared a series of sulfides by the reaction of thiols with chlorides in the K_2CO_3/CH_3CN system.[37] In this procedure, we found, in the system, disulfides can be synthesized in excellent yields by oxidation of the corresponding thiols. In this paper, we report a simple aerobic oxidative coupling of thiols to disulfides using K^+/CH_3CN system at room temperature with good to excellent yields, and examined the effect of the solvent and base on the oxidation of thiols in detail.

RESULTS AND DISCUSSION

4-Methylthiophenol (**1a**) was selected as a model substrate for optimization studies. In a typical reaction, a mixture of 1 mmol 4-methylbenzenethiol (**1a**), 1 mmol base and 5 mL of solvent were stirred at room temperature in a round bottom flask without an air bubbler.

Initially, various solvents and bases were examined to facilitate this transformation. As results showed that acetonitrile was most effective solvent and itself had some catalytic activity for the oxidation in presence of air (Table I, entry 6). The examination of base effect showed that the catalytic activity of K_2CO_3 was the highest in acetonitrile (Table I, entries 1 and 6–8). Even the reaction was completed in 40 min with catalytic amount of K_2CO_3 to give the correspounding disulfides in quantitative yield (Table I, entry 10). To prove the significance of O_2

TABLE I The Effects of the Solvent and Base on the Oxidation of Thiols

Entry	Base	Solvent	Time
1	K_2CO_3	CH_3CN	30 min[a]
2	K_2CO_3	CH_2Cl_2	$\gg$3 h[b]
3	K_2CO_3	CH_3Cl	$\gg$3 h[b]
4	K_2CO_3	CH_3OH	3 h[a]
5	K_2CO_3	benzene	3 h (trace)
6	—	CH_3CN	>7d
7	Et_3N	CH_3CN	6 h[a]
8	Pyridine	CH_3CN	>6 h[b]
9	Na_2CO_3	CH_3CN	4 h[a]
10	K_2CO_3 (Cat.)	CH_3CN	40 min[a]
11	K_2CO_3 (oxygen-free)	CH_3CN	1h[b] (trace)

[a]The reaction was completed in the mentioned time.
[b]The reaction was not completed in the mentioned time.

TABLE II Synthesis of Disulfides 2a Using Various K^+/CH_3CN System at Room Temperature

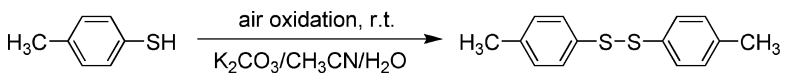
Entry	Base	Time	Yield of **2a** (%)
1	KF	1 h	99[b] (99.7)[e]
2	KCl	24 h	8.79[d]
3	KBr	24 h	91[a] (98.9)[e]
4	KI	48 h	trace
5	KI + Et_3N	1 h	99[a] (99.4)[e]
6	KI (Cat.) + Et_3N	1 h	95[a] (99.9)[e]
7	K_2CO_3	30 min	quant.[b] (99.7)[c]

[a]Isolated yield by silica-gel column chromatography.
[b]Isolated yield by direct filtration, evaporation.
[c]Purity assessed by HPLC.
[d]Yield by GC.
[e]Purity assessed by GC.

in the reactions, we conducted a oxygen-free operation, in which a mixture of thiophenol and K_2CO_3 in acetonitrile without O_2 were stirred. The oxidation hardly occur in the absence of O_2, which indicated that O_2 acted as the oxidant in the oxidation process.

Next, the coupling of 4-methylbenzenethiol (**1a**) using a series of potassium halides in a neutral or near-neutral medium was carried out to expand the reaction conditions. The results indicated that potassium salts indeed promoted the reaction, and the order of the catalytic activity of potassium salts was KF≫KBr≫KCl>KI (Table II, entries 1–4). Aromatic thiol **1a** was converted to the corresponding disulfide in 1 h in the presence of KF and in 24 h in the presence of KBr at room temperature. In the presence of KI, **1a** was not converted into corresponding disulfide completely even after 48 h because of the weak acidity of the reaction solution. However, the addition of Et_3N was found to be effective to promote the reaction. With 1 mmol **1a** and 1 mmol KI in acetonitrile, when the reaction system was adjusted to pH = 8∼9 using Et_3N (2 drops), the reactions were completed within 1 h, and the disulfide **2a** was obtained in excellent yield after chromatographic purification (Table II, entry 5). In the case of the reaction with 1 mmol **1a**, catalytic amount of KI (0.1 mmol) and Et_3N (2 drops) was sufficient, and the disulfide **2a** was obtained in excellent yield after chromatographic purification (Table II, entry 6). From these results it was concluded that, in the K^+/CH_3CN system, weak alkaline medium could increased the oxidation rate greatly. Furthermore, highly pure disulfides were also obtained without tedious column chromatographic purification, the reaction mixture was filtered, the resulting residue

TABLE III Reaction of Thiol 1a in $K_2CO_3/CH_3CN/H_2O$ System at Room Temperature



1a **2a**

Entry	VH_2O/VCH_3CN (%)	Time	Yield of 2a (%)
1	5	1 h	45[a] (99.7)[b]
2	5	6h	quant[a](99.6)[b]
3	20	6h	quant[a](99.7)[b]
4	40	6h	22[a] (99.8)[b]
5	40	24 h	60[a] (98.1)[b]

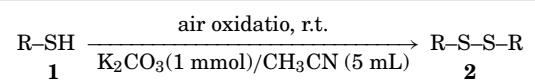
[a]Isolated yield by direct filtration after adding water.
[b]Purity assessed by GC.

was washed with petroleum ether (2 × 5 mL), then evaporation of the filtrate under reduced pressure to obtain highly pure disulfides in good yields (Table II, entries 1 and 7). Additionally, the yields of disulfides were not affected by the reaction temperature.

Further, we examined the reaction in a mixture solvent of acetonitrile and water, these results are summarized in Table III. In these cases, it took longer time to complete the reaction (Table III, entries 2 and 3), still affording the desired disulfides in high yields. In the case of entries 4 and 5, the reactions could not reach completion and only about 60% yield of the disulfide was obtained even with a prolonged reaction time. However, in these cases, after the reaction completed, the disulfide could precipitated out from the reaction mixture completely by adding a certain volume water, then highly pure disulfides were isolated by simple filtration.

The results above showed that the K_2CO_3/CH_3CN system was the most suitable for the aerobic oxidative coupling of thiols to disulfides. Finally, the oxidative coupling of other thiols were carried out according to established methods. As shown in Table IV, the desired disulfides **2** were obtained in 90–99% yields after silica-gel column chromatography purification (Table IV, entries 1–6). And the results showed that the reactions of aromatic thiols bearing electron-donating groups were faster, and the reactions of thiophenols were faster than that of benzyl mercaptan. Regrettably, when aliphatic thiol **1g** was used, the reactivity was significantly decreased, and the reaction could not reach completion under the conditions described above (Table IV, entry 7), which was on the contrary to the general notion that the oxidation reaction of aliphatic thiols is faster than that of aromatic thiols.

TABLE IV Oxidative Coupling of Thiols 1 to the Corresponding Disulfides 2 in K_2CO_3/CH_3CN System at Room Temperature



Entry	Thiols 1		Time	Disulfide 2	Yield (%)[a]
1	**1a**	*p*-Tolylthiol	30 min	**2a**	96
2	**1b**	Phenylthiol	30 min	**2b**	94
3	**1c**	p-methoxyphenylthiol	20 min	**2c**	95
4	**1d**	3,4-difluorophenylthiol	7 h	**2d**	90
5	**1e**	4-Chlorobenzyl mercaptan	24 h	**2e**	90
6	**1f**	4-*tert*-butylbenzyl mercaptan	2.5 h	**2f**	91
7	**1g**	n-$C_{12}H_{25}SH$	24 h	**2g**	16.4[b]

[a]Isolated yield by silica-gel column chromatography.
[b]Yield by GC.

CONCLUSION

In conclusion, we have introduced a simple, mild, clean and efficient aerobic oxidative coupling of thiols to disulfides using K^+/CH_3CN system. Compared with the previously reported the aerobic oxidation of thiols, the procedure have have the following advantages: (1) potassium salts as catalysts is more available; (2) simplicity of the reaction conditions without an air bubbler; (3) neutral or weak alkaline of the reaction medium; (4) the reaction is insensitive to water. So the oxidation method meets the needs of contemporary green chemistry and is suitable for practical synthesis.

EXPERIMENTAL

Melting points were conducted on a Yanaco MP-500 micro melting-point apparatus. ^1H NMR spectra were recorded in $CDCl_3$ as solvent on Bruker AC-300 and Bruker AC-400 instrument using TMS as an internal standard. Elemental analysis was performed on a Yanaco CHN Corder MF-3 automatic elemental analyzer. GC analyses of the compounds were performed on an Agilent Technologies 6890 N Network GC System (with a TCZWAX capillary 30m column).

General Procedure for the Oxidation of Thiols

A mixture of thiol (1.0 mmol), potassium carbonate (1.0 mmol) in acetonnitrile (5 mL) is strirred at room temperature and access to atmosphere in a glass reactor equipped without an air purge. The completion of reaction is monitored by TLC. The reaction mixture is filtered, and evaporation of the filtrate under reduced pressure followed by preparative thin layer chromatography on silica gel afforded the pure products.

2a. Yield: 96% Mp 40–43°C (Lit.[38] mp 42–43°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.340 (s, 6H, CH_3), 7.127 (d, 4H, Ph, $J = 6.0$ Hz), 7.406 (d, 4H, Ph, $J = 6.3$ Hz).

2b. Yield: 94% Mp 64–66°C (Lit.[39] mp 61–62°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.198–7.510 (m, 8H, Ph).

2c. Yield: 95% Mp 35–36°C (Lit.[40] mp 40–42°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.795 (s, 6H, OCH_3), 6.830 (d, 4H, Ph, $J = 8.4$ Hz), 7.381–7.403 (m, 4H, Ph).

2d. Yield: 90% oil liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.822–6.887 (m, 4H, Ph), 7.467–7.525 (m, 2H, Ph).

2e. Yield: 90% Mp 56–58°C (Lit.[41] mp 59–60°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.569 (s, 4H, CH_2), 7.414–7.161 (m, 4H, Ph), 7.282–7.303 (m, 4H, Ph).

2f. Yield: 91% Mp 65–66°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.310 (s, 18H, CH_3), 3.593 (s, 4H, CH_2), 7.173 (d, 4H, Ph, $J = 8.0$ Hz), 7.340(d, 4H, Ph, $J = 8.4$ Hz). Anal. calcd. for $C_{22}H_{30}S_2$: C, 73.68; H, 8.43. Found: C, 73.38; H, 8.33.

2g. Yield: 16.4% Mp 28–29°C (Lit.[42] mp 29–31°C).^{1}H NMR (300 MHz, $CDCl_3$): δ 0.881, (t, 6H, CH_3, $J = 6.3$), 1.262–1.398 (m, 36H, CH_2), 1.620–1.717 (M, 4H, CH_2), 2.655, 2.680, 2.704 (t, 3H, CH_2, $J = 7.2$).

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