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2,6-Dicarboxypyridinium chlorochromate: an efficient and selective reagent for the oxidation of thiols to disulfides and sulfides to sulfoxides

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Abstract—2,6-Dicarboxypyridinium chlorochromate (2,6-DCPCC) was found to be an efficient reagent for the conversion of thiols to disulfides and sulfides to sulfoxides under neutral and anhydrous conditions in good to excellent yields. Selective oxidation of thiols in the presence of sulfides at room temperature is also observed with this reagent.

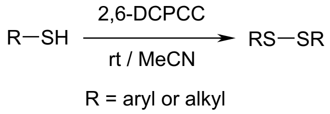
Among several methods of preparing disulfides, most methods involve oxidation of thiols. Oxidation of thiols to disulfides without over oxidation is an important process in organic chemistry and biochemistry, which has been extensively investigated over the years. Disulfide bond formation is important in peptides[1] and bioactive molecules.[2] This conversion has been accomplished using reagents such as molecular oxygen,[3a] metal ions,[3b] $Bu_3SnOMe/FeCl_3$,[3c] nitric oxide,[3d] halogens,[3e–h] sodium perborate,[3i] borohydride exchange resin (BER)-transition metal salt system,[3j] a morpholine iodine complex,[3k] PCC,[3l] ammonium persulfate,[3m] $KMnO_4/CuSO_4$,[3n] H_2O_2,[3o] solvent free permanganate,[3p] PVP–N_2O_4,[3q] and cesium fluoride-Celite, O_2 system.[3r]

Sulfoxides are useful in organic synthesis as an activating group. They have been utilized extensively in carbon–carbon bond forming reactions.[4] The oxidation of sulfides to sulfoxides has been the subject of extensive investigations. The biggest difficulty associated with the oxidation of sulfides to sulfoxides is the susceptibility of sulfoxide to undergo further oxidation in the reaction mixture to produce a sulfone.[5] A number of procedures for this transformation from sulfides include treatment with halogens,[6a] *t*-butyl hypochlorite,[6b] *N*-halosuccinimides,[6c] hydrogen peroxide,[6d] *m*-chloroperbenzoic acid,[6e] sodium metaperiodate,[6f] nitrogen tetroxide,[6g] manganese oxide/trimethylchlorosilane,[6h] tetrabutylammonium peroxydisulfate,[6i] CAN,[6j] $NaClO_2$/Mn(III) catalyst/alumina,[6k] and magnesium monoperoxyphthalate (MMPP).[6l] However some of these methods have disadvantages such as requiring strong oxidizing agents, strongly acidic or basic media, over-oxidation, use of expensive reagents, long reaction times, low yields of products, and acidic work-ups. Therefore the introduction of a clean, mild, and efficient method to synthesize aliphatic, aromatic, and heteroaromatic disulfides and sulfoxides is still needed.

Recently, we introduced 2,6-dicarboxypyridinium chlorochromate as an efficient reagent for oxidation of alcohols, trimethylsilyl ethers, THP ethers, and oximes to the corresponding carbonyl compounds under nonaqueous conditions.[7] We have now explored its utility for the oxidation of thiols and sulfides to disulfides and sulfoxides, respectively, under mild reaction conditions.

Thiols were oxidized in acetonitrile with 2,6-DCPCC to give the corresponding disulfides at room temperature (Scheme 1).

The results presented in Table 1 indicate that the present method is equally applicable for the oxidative coupling



Scheme 1.

Keywords: 2,6-Dicarboxypyridinium chlorochromate; Oxidation; Thiols; Sulfides; Disulfides; Sulfoxides.

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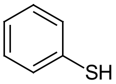
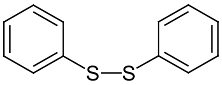
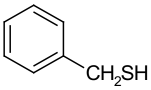
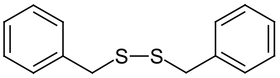
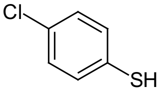
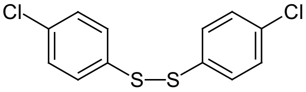
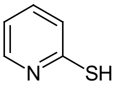
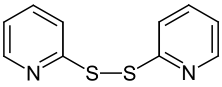
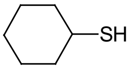
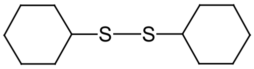
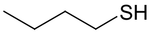
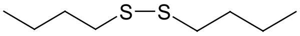
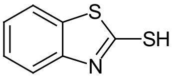
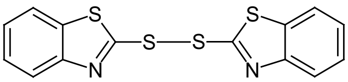
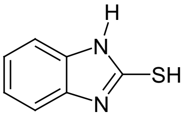
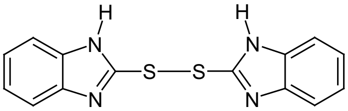
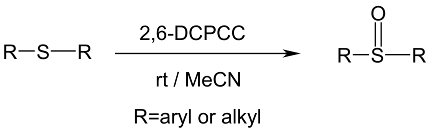
Table 1. Coupling of thiols using 2,6-DCPCC

Entry	Substrate	Product	Time (min)	Yield (%)[a]
1			10	93
2			8	96
3			20	88
4			13	95
5			18	91
6			14	90
7	HS–CH$_2$–CO$_2$H	HO$_2$C–CH$_2$–S–S–CH$_2$–CO$_2$H	15	90
8			27	94
9			30	93

[a] Yield refers to isolated product; all products were identified by comparing IR, NMR, and TLC with those of authentic samples.



Scheme 2.

of alkyl (entries 2, 5–7), aryl (entries 1, 3), and heterocyclic (entries 8, 9) thiols. The reactions are usually carried out under mild conditions with excellent yields and simple work-up: only filtration is required to remove the reagent and evaporation of the filtrate afforded pure products.

Sulfides are also oxidized with this reagent to the corresponding sulfoxides in 80–96% yield in acetonitrile (Scheme 2).

The results of this study are presented in Table 2. This reaction system can be applied to the oxidation of many types of sulfide such as dialkyl sulfides (entries 2, 5, 11–14), alkyl aryl sulfides (entries 1, 3, 4, 6–8), and diaryl sulfides (entry 9). Even an aryl sulfide with two strong electron withdrawing groups (NO$_2$) (entry 9) reacted smoothly to give the corresponding sulfoxide in 80% yield.

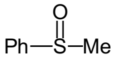
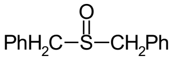
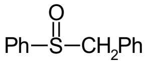
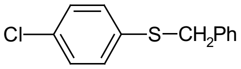
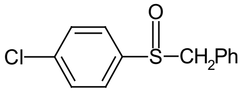
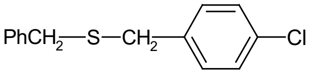
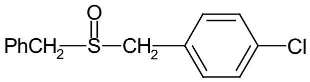
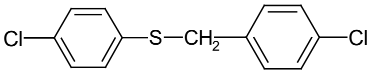
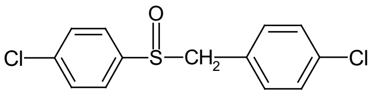
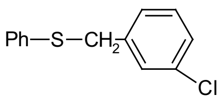
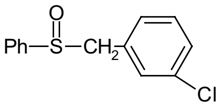
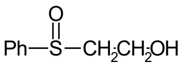
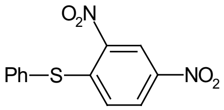
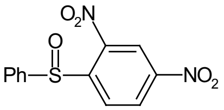
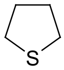
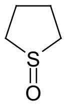
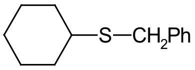
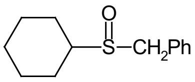
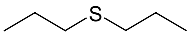
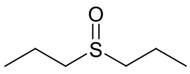
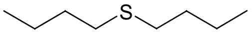
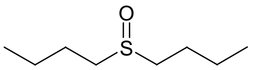
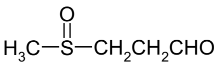
Although thiols underwent oxidation at room temperature in less than 30 min, the oxidation of sulfides was slow and required a higher number of equivalents of reagent.

This reagent can also selectively oxidize thiols in the presence of sulfides at room temperature. When a mixture of equimolar amounts of thiols **1** or **5** in the presence of sulfides **2** or **6** were treated with 2,6-DCPCC, only the thiols were selectively oxidized to the corresponding disulfides and the sulfides remained largely unchanged (Scheme 3).

In order to show the advantages and drawbacks of this reagent over some other oxidants, we have compared some of our results with those reported in the literature in Table 3.

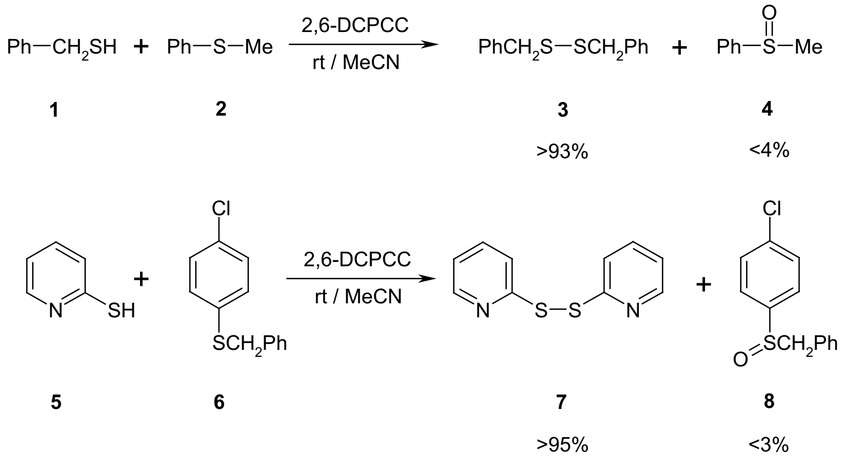
In conclusion, we have shown that 2,6-DCPCC is an efficient, rapid, mild, and inexpensive reagent for the oxida-

Table 2. Oxidation of sulfides to sulfoxides using 2,6-DCPCC

Entry	Substrate	Product	Time (min)	Yield (%)[a]
1	Ph–S–Me	 $Ph-\overset{O}{\overset{\Vert}{S}}-Me$	10	95
2	$PhH_2C–S–CH_2Ph$	 $PhH_2C-\overset{O}{\overset{\Vert}{S}}-CH_2Ph$	8	96
3	$Ph–S–CH_2Ph$	 $Ph-\overset{O}{\overset{\Vert}{S}}-CH_2Ph$	9	94
4			12	93
5			11	92
6			15	85
7			16	88
8	$Ph–S–CH_2{\cdot}CH_2{\cdot}OH$	 $Ph-\overset{O}{\overset{\Vert}{S}}-CH_2CH_2OH$	11	93
9			50	80
10			14	95
11			16	90
12			12	93
13			15	93
14	$H_3C–S–CH_2CH_2CHO$	 $H_3C-\overset{O}{\overset{\Vert}{S}}-CH_2CH_2CHO$	16	93

[a] Yield refers to isolated product; all products were identified by comparing IR, NMR, and TLC with those of authentic samples.

tion of aliphatic, aromatic, and heteroaromatic thiols and sulfides to the corresponding disulfides and sulfoxides. This reagent oxidizes thiols almost quantitatively irrespective of the presence of sulfides. We consider that our procedure represents a useful addition to the array of procedures for the oxidation of thiols and sulfides.



Scheme 3.

Table 3. Camparison of 2,6-DCPCC with some of the other reagents for oxidation of thiols and sulfides

Substrate	Conditions	Time (min)/Yield (%)	Reagent	Reference
PhSH	CH_3CN/rt	8/93	2,6-DCPCC	—
PhSH	CH_3CN/rt	120/99	$Bu_3SnOMe/FeCl_3$	3c
PhSH	CH_2Cl_2/rt	114/97	PCC	3l
PhSH	Solid state	10/79	$(NH_4)_2S_2O_8$	3m
PHSH	CH_3CN/20 °C	270/93	Caro's acid/SiO_2	8
PhSMe	CH_3CN/rt	10/95	2,6-DCPCC	—
PhSMe	CH_3OH/20 °C	60/99	MnO_2–TMSCl	6h
PhSMe	CH_2Cl_2/rt	90/98	$(n\text{-}Bu_4N)_2S_2O8$	6i
PhSMe	CH_2Cl_2/rt	60/100	CAN	6j
PhSMe	CH_2Cl_2	15/89	$NaClO_2$/Alumina	6k

General procedure for the oxidation of thiols with 2,6-DCPCC. In a round-bottomed flask, a solution of thiol (1 mmol) in MeCN (10 mL) was treated with 2,6-dicarboxypyridinium chlorochromate (1 mmol) and the mixture stirred at room temperature. The progress of the reaction was monitored by GC or TLC. The reaction mixture was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was washed with water (3 × 10 mL), dried, and evaporated to give the corresponding disulfide in almost pure form. If necessary, the product was purified by column chromatography (eluent: hexane/CH_2Cl_2).

General procedure for the oxidation of sulfides with 2,6-DCPCC. In a round-bottomed flask, a solution of sulfide (1 mmol) was treated with 2,6-dicarboxypyridinium chlorochromate (2 mmol) and the mixture was stirred at room temperature. The progress of the reaction was monitored by GC or TLC. The reaction mixture was filtered and the solid material was washed with CH_2Cl_2 (20 mL). If necessary, the product was purified by column chromatography (eluent: hexane/EtOAc).

Acknowledgement

Financial support of this work from the Research Council of Mazandaran University is gratefully acknowledged.

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