SHORT PAPER

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Oxidation of thiols to the corresponding disulfides with tetramethylammonium chlorochromate under non-aqueous conditions†

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This paper describes the preparation of tetramethylammonium chlorochromate (TMACC) as an efficient and mild reagent for oxidation in refluxing acetonitrile of a variety of aromatic and aliphatic thiols, giving the corresponding disulfides; the experimental procedure is simple, and the products are easily isolated in excellent yields.

Keywords: tetramethyammonium chlorochromate, thiols

The oxidative coupling of thiols to their corresponding disulfides under mild conditions is of significant importance from a biological and practical point of view.[1–3] Since thiols are among the functional groups which can be over-oxidised, extensive research has been performed to control their oxidation.[4–11]

The oxidation of thiols **2** to disulfides **3** is a characteristic reaction, and further oxidation to disulfide *S*-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), and sulfonic acids is possible. Weak S–S bonds in these compounds impart high reactivity,[12] and in natural products, these moieties and related cyclic analogues are associated with interesting biological activity and DNA-cleaving properties.[13–15]

In connection with our ongoing programme to introduce new reagents for the oxidation of organic compounds under mild conditions,[16,17] we wish to report the preparation of tetramethylammonium chlorochromate **1** and application of this inexpensive and mild reagent for oxidative coupling of a variety of aliphatic and aromatic thiols and aliphatic dithiols to their corresponding acyclic and cyclic disulfides. This reagent is readily prepared by the dropwise addition of CrO_3 in aqueous 6 M HCl to an aqueous solution of tetramethylammonium chloride at room temperature. Filtration and drying of the precipitates produced an orange powder, which could be stored for months without losing its oxidation ability. This reagent is quite soluble in methylene chloride, chloroform, acetone, THF, DMF, DMSO, and acetonitrile and insoluble in non-polar solvents, such as carbon tetrachloride, *n*-hexane, and diethyl ether (Scheme 1).

This method is a remarkably effective methodology for oxidising aliphatic and aromatic thiols to disulfides. This reagent also exhibits a synthetically valuable method for producing cyclic disulfides from dithiols. The oxidation of dithiols results in the formation of cyclic and/or polymers disulfides. The polymers result from intermolecular oxidation, while the cyclic disulfides arise from intramolecular oxidative coupling of dithiols. For example, oxidative coupling of 1,4-benzenedimethanethiol gives only polymeric product (Table 1), while 1,3-dithiol gives 65% cyclic disulfides and 35% polymeric products. The butane 1,4-dithiol gives only cyclic disulfides in 96% yields. It was found that further oxidation of disulfide to *S*-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), and sulfonic acid did not occurr. A series of thiols was oxidised to disulfides rapidly by this reagent (Table 1). Primary alcohol, amine, carboxylic acid, ester, and methoxy functional groups were unaffected during the oxidation of the thiols. The dithiols were oxidised to the corresponding cyclic disulfides in good yields (Scheme 2 and Table 1).

In conclusion, in this study we have introduced a new and mild reagent for the preparation of tetramethylammonium chlorochromate **1**. The stability, ease of preparation, straightforward work-up, mild reaction conditions, high yields of the products, and reaction under non-aqueous conditions make this method a useful one for oxidation of thiols and dithiols to disulfides.

Experimental

General: All yields refer to isolated products. Products were characterised by comparison with authentic samples (IR and ^{1}H NMR spectrum, melting and boiling point, TLC).[5-7, 19-24] All ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and CCl_4 relative to TMS (0.00 ppm).

Safety note: Chromium compounds can cause primary irritation, ulceration and allergic eczema when directly contacted with the skin and nasal and pulmonary irritation,with possible bronchogenic carcinoma upon breathing of chromate dust. Oral ingestion produces violent gastrointestinal irritation with vomiting and diarrhoea.

Preparation of tetramethylamonium chlorochromate 1 (TMACC): A solution of tetramethylamonium chloride (10.95 g, 100 mmol) in 100 ml of water was prepared, and then CrO_3 (10.0 g, 100 mmol) in HCl 6 M (50 ml) was added dropwise to the above solution and

$$Me_4N^+Cl^- + CrO_3\ (HCl\ 6\ M) \xrightarrow[96\%]{H_2O/10\ min} Me_4N.CrO_3HCl \quad \mathbf{1}$$

Scheme 1

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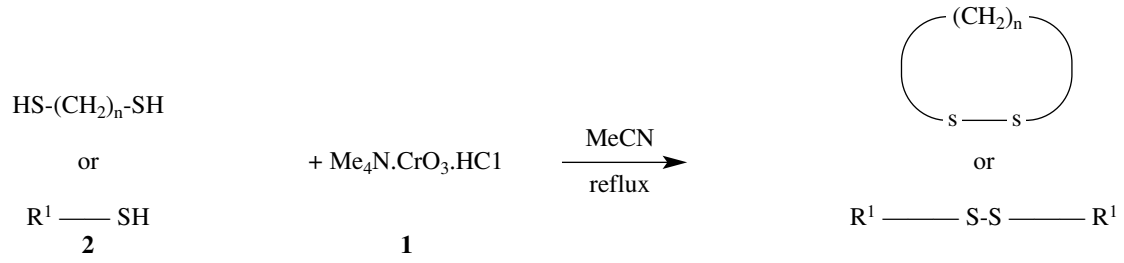
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



R^1 = Alkyl, or Aryl and n = 3 or 4

Scheme 2

Table 1 Oxidation of thiols **2** with reagent **1** to disulfides **3** in refluxing acetonitrile [a, b]

Reactant **(2)**	Product (3)	Reaction time/h	Yield[c]/%	M.p. or B.p./mmHg°C (Lit.) [5–7,19–24]
C_6H_5SH	$C_6H_5SSC_6H_5$	1.1	98	59–61 (59–60)
4-MeC_6H_4SH	4-$MeC_6H_4SSC_6H_4Me$-4	1.3	92	47–48 (46–48)
4-$MeOC_6H_4SH$	4-$MeOC_6H_4SSC_6H_4OMe$-4	1.4	88	44–45 (43.8)
4-$NH_2C_6H_4SH$	4- $NH_2C_6H_4SSC_6H_4$ NH_2-4	1.3	85	75–77 (76–77)
3-MeC_6H_4SH	3-$MeC_6H_4SSC_6H_4Me$-3	1.2	94	–21 (–21)
4-ClC_6H_4SH	4-$ClC_6H_4SSC_6H_4Cl$-4	0.9	98	72–73 (72–73)
2-$MeOOCC_6H_4SH$	2-$MeOOCC_6H_4SSC_6H_4COOMe$-2	0.8	96	198–191 (193)
$C_6H_5CH_2SH$	C_6H_5 CH_2SS $CH_2C_6H_5$	1.4	91	69–70 (69–70)
4-$NO_2C_6H_4SH$	4- $NO_2C_6H_4SSC_6H_4$ NO_2-4	0.7	96	177–178 (182)
2-PyridylSH	2-PyridylSS-Pyridyl-2	0.8	90	52–53 (52–53)
4-PyridylSH	4-PyridylSS-Pyridyl-4	1.0	93	76–77 (76–77)
CyclopentylSH	CyclopentylSSCyclopentyl	1.7	90	105–106 (107–108)
CyclohexylSH	CyclohexylSSCyclohexyl	1.8	85	124 129 (125–130)
HO-CH_2CH_2SH	HO-$CH_2CH_2SSCH_2CH_2OH$	2.2	86	156–148/2 (158–163/3.5)
$HOOCCH_2CH_2SH$	$HOOCCH_2CH_2SSCH_2CH_2COOH$	2.0	89	157–159 (157–159)
$HOOCCH_2SH$	$HOOCCH_2SSCH_2COOH$	2.0	93	138–139 (140)
$CH_3(CH_2)_3SH$	$CH_3(CH_2)_3SS(CH_2)_3CH_3$	1.8	89	94-96/6 (86/3.5)
$CH_3(CH_2)_4SH$	$CH_3(CH_2)_4SS(CH_2)_4CH_3$	2.0	87	117–119/6 (90-92/1)
$CH_3(CH_2)_6SH$	$CH_3(CH_2)_6SS(CH_2)_6CH_3$	2.0	90	152–154/6 (143-147/5)
$CH_3(CH_2)_7SH$	$CH_3(CH_2)_7SS(CH_2)_7CH_3$	2.0	92	152–154/6 (143-147/5)
1-$HSCH_2C_6H_4CH_2SH$-4	(-$SCH_2C_6H_4CH_2S$-)$_n$	1.2	95	–
$SH(CH_2)_3SH$	1,5-Cyclopentanedisulfide	2.0	65	45–47/6 (–)
	(+ (-$SH(CH_2)_3S$-)$_n$)		(35 Polymer)	65–70 (71–73)
$SH(CH_2)_4SH$	1,6-Cyclohexanedisulfide	2.0	96	(32–33)

[a]Confirmed by comparison with authentic samples (IR, TLC, and NMR). [b]Oxidant/thiol (1.0:1.0). [c]Yield of isolated pure product after chromatography or distillation.

stirred for 10 min. at room temperature. The resulting orange precipitate was filtered and washed with cooled distilled water (2 × 50 ml), and dried in a desiccator under vacuum over calcium chloride to afford an orange powder (20.2 g, 96% yield), which decomposed at 210–212 ºC to a dark brown material. H NMR: δ 3.58 (s). Anal Calcd for $C_4H_{13}ClCrNO_3$: C, 22.80; H 6.18%. Found: 22.96; H, 6.28%.

General procedure: Oxidation of thiols with TMACC 1: In a round-bottomed flask (25 ml) equipped with a reflux condenser and a magnetic stirrer, a solution of thiol (1 mmol) in acetonitrile (5 ml) was prepared. TMACC (0.21 g, 1 mmol) was added to the solution and refluxed for the time specified in Table 1. The reaction progress was followed by TLC (eluent: cyclohexane/EtOAc: 8:2). The reaction mixture was then cooled to room temperature and the solid was separated through a short pad of silica gel and washed with acetonitrile (15 ml). The filtrate was evaporated and the resulting crude material was dissoved in CH_2Cl_2 and washed with 5% NAOH solution. The organic layer was dried ($MgSO_4$) and evaporated with a rotary evaporator and purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent (10:90). Pure disulfides were obtained in 65–98% yields (Table 1).

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