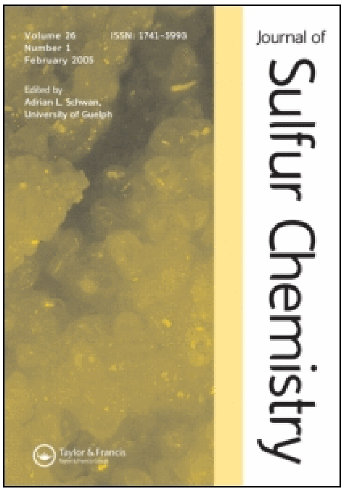

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RESEARCH ARTICLE

Oxidative coupling of thiols to disulfides in solution and under microwave radiation with tripropylammonium chlorochromate

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A mild and efficient method for the oxidative coupling of thiols by tripropylammonium chlorochromate in solution and in solution under microwave radiation is reported. Tripropylammonium chlorochromate is an efficient and new reagent, is easily prepared, and rapidly oxidizes thiols to the corresponding disulfides. The reactions proceed cleanly and stop at the disulfide stage without over-oxidation to side-products. The simple procedure and work-up, short reaction times, and excellent yields are all advantages of this reagent.

Keywords: Thiol; Oxidation; Disulfide; Tripropylammonium chlorochromate; Solution; Microwave

1. Introduction

The oxidation of organic substrates in aprotic solvents, under mild and neutral conditions, is important in modern organic synthesis. Therefore, the search for new oxidizing agents is of interest to synthetic organic chemists. As such, many useful reagents have been developed in recent years [1]. Disulfides are one of the most important classes of organic sulfur compounds, possessing noteworthy reactivity in biochemistry [2] and as key intermediates in a wide variety of organic synthetic routes [3–6]. The catalytic conversion of thiols into disulfides in the oil industry [7, 8] and the industrial applications of disulfides in vulcanization of rubbers and elastomers prompted us to investigate the introduction and applications of a new member reagent for the oxidation of thiols to the corresponding disulfides.

Many stoicheiometric reagents like manganese dioxide [9], dichromates [10], halogenosilane–chromium trioxide [11], diethyl azodicarboxylate [12], nickel peroxide [13], chromium peroxide [14], diaryl telluroxide [15], tetrabutylammonium ceric(IV) nitrate [16], sodium perborate [17], silver trifluoromethanesulfonate [18], and supported permanganate [19] have been developed for this transformation. These reagents suffer from either one or more of the

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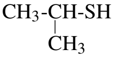
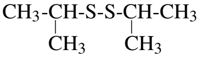
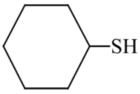
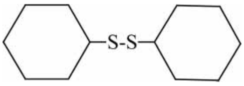
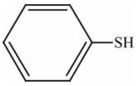
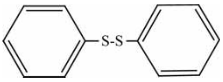
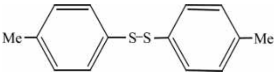
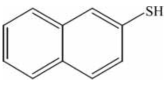
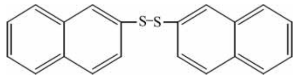
following disadvantages: low availability of the reagent, cumbersome work-up procedure, high cost of the reagent, over-oxidation, or oxidation of other functional groups in the presence of the thiol group. As a result, there is still a need for the development of general, efficient, and new reagents for the synthesis of disulfides from the corresponding thiols under mild reaction conditions. These reactions are not only of interest from an ecological viewpoint, but also in many cases offer considerable synthetic advantages in terms of the yield, selectivity, and simplicity of the reaction procedure. In this respect, we wish to report that tripropylammonium chlorochromate (TriPACC) is able to oxidize thiols to their disulfides efficiently under different reaction conditions.

2. Results and discussion

TriPACC is an easily prepared reagent, yet no examples of its applications in organic synthesis seem to have been recorded. The oxidative coupling of thiols with this reagent was investigated in dichloromethane at room temperature and in dichloromethane solution under microwave radiation. As shown in table 1, a series of aliphatic and aromatic thiols were treated with 0.5 molar equivalents of the reagent to afford the corresponding disulfides in excellent yields. This oxidation was also performed under microwave conditions with 0.5 molar equivalents of the reagent. The results show that, under microwave conditions, the reaction times are significantly shorter. This advantage makes this procedure a valuable method of preparation of disulfides (Scheme 1).

Table 1. Oxidative coupling of thiols with TriPACC in solution and under microwave conditions.

		Solution			Solution under microwave irradiation	
	Substrate	Time (t/min)	Product	Yield (%)	Time (t/min)	Yield (%)
1	 $CH_3\text{-}\underset{CH_3}{CH}\text{-}SH$	135	 $CH_3\text{-}\underset{CH_3}{CH}\text{-}S\text{-}S\text{-}\underset{CH_3}{CH}\text{-}CH_3$	85	10	85
2	$n\text{-}C_5H_{11}\text{-}SH$	100	$C_5H_{11}\text{-}S\text{-}S\text{-}C_5H_{11}$	86	9	87
3	$n\text{-}C_8H_{17}\text{-}SH$	75	$C_8H_{17}\text{-}S\text{-}S\text{-}C_8H_{17}$	90	7	92
4		140		87	13	85
5	$HOOC\text{-}CH_2\text{-}SH$	200	$HOOC\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}COOH$	89	18	89
6		30		90	3	92
7		25		85	3	91
8		45		87	5	96

$$\mathrm{RSH} \xrightarrow[\text{A or B}]{\text{TriPACC}} \mathrm{RSSR}$$

TriPACC: $(C_3H_7)_3NH[CrO_3Cl]$
A: Dichloromethane, room temperature
B: Dichloromethane, room temperature, microwave

SCHEME 1.

Disulfides are cleanly produced with yields consistently greater than 85%. The reactions occur in a controlled manner, stopping at the disulfide stage. Over-oxidation was not observed, under either set of conditions.

Overall, TriPACC acts as a simple, efficient, and fast oxidizing reagent for coupling thiols. The easy procedure, simple work-up, easy preparation of the reagent, short reaction times, and excellent yields of the products will make this reagent a useful addition to available oxidants for the organic chemist.

3. Experimental

3.1 *Materials and instruments*

CrO_3 (Merck, P.A.) was used without further purification. Solvents were purified by standard methods. IR spectra were recorded as KBr disks on a Shimadzu model 420 spectrophotometer. UV/Visible measurements were made on a Uvicon model 922 spectrometer. ^1H and ^{13}C NMR acquisitions were carried out on a Bruker AVANCE DRX 500 spectrometer at 500 and 125 MHz, respectively. Chromium was estimated iodometrically. In the case of the reduced product of the oxidant, chromium was determined after oxidation with acidic peroxodisulfate ($K_2S_2O_8$) solution. Combustion analyses were obtained from the Microanalytical Laboratories, Department of Chemistry, OIRC, Tehran. Mps were measured on an Electrothermal 9100 melting point apparatus and are uncorrected. A Microsynth Milestone laboratory microwave oven operating at 300 W was used for these reactions.

3.2 *Preparation of tripropylammonium chlorochromate (TriPACC)*

Chromium(VI) oxide (10.0 g, 0.10 mol) was dissolved in water (minimum amount such as 20 ml) in a beaker and 37% hydrochloric acid (2.51 ml, 0.15 mol) was added to the stirred solution at 0 °C. To the resultant clear orange solution was added tripropylamine (1.43 ml, 0.10 mol) dropwise stirring to this stirred solution over a period of 0.5 h, and stirring was continued for 0.5 h at −4 °C. The precipitated orange solid was isolated by filtration, washed with anhydrous diethyl ether (3 × 60 ml) and dried *in vacuo* for 2 h at room temperature (26.55 g, 95%); mp 135 °C [For $C_9H_{22}ClCrNO_3$: Calc.: C, 38.64; H, 7.87; N, 5.00. Found: C, 37.93; H, 7.75; N, 4.88%]. IR (KBr) 901 $\nu_1(A_1)$ or $\nu(CrO_3)$, 432 $\nu_2(A_1)$ or ν(Cr-Cl), and 949 cm^{-1} $\nu_4(E)$ or $\nu(CrO_3)$. UV/Visible, ^{13}C NMR, and ^1H NMR results were all consistent with the TriPACC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of a 0.01 M solution of TriPACC in water was 2.9.

3.3 *General procedure for oxidative coupling of thiols in dichloromethane*

To a stirred solution of 4-methylbenzenethiol (0.248 g, 2 mmol) in dichloromethane (5 ml) was added TriPACC (0.279 g, 1 mmol), and the mixture was stirred at room temperature for

25 min. A solid was formed and was treated with a 1:1 mixture of diethyl ether and water (2 ml). The reaction mixture was extracted with diethyl ether (3 × 10 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by recrystallization or chromatography on silica gel afforded the pure disulfide in 85% (0.209 g) yield, and which was characterized by NMR and IR spectroscopy; mp 45 °C (Lit. [20], 45–46 °C).

3.4 *General procedure for oxidative coupling of thiols under microwave radiation*

To a stirred suspension of TriPACC (1 mmol) in dichloromethane (generally 5 ml) was added dropwise a solution of the substrate in the minimum amount of dichloromethane, the molar ratio of substrate to oxidant being 1:2. The mixture was subjected to microwave irradiation for the time indicated in table 1 [the completion of the reaction was followed by UV/visible spectrophotometry and TLC using diethyl ether/light petroleum (60/40) as developer]. The mixture was diluted with diethyl ether (1:1 vol/vol) and filtered through a short column of silica gel to give a clear solution, which was evaporated and the residual product purified by distillation, recrystallization, or column chromatography.

To monitor the reaction by UV/visible spectrophotometry, an amount of the oxidant was extracted during the reaction and was measured spectrophotometrically at 355 nm. A very small magnetic stirrer was placed in the cell (10 mm quartz cell) compartment at the bottom of sample cell in the spectrophotometer to stir the solution under study in the cell. The reaction mixtures remained homogenous in the solvent system used.

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