## Microwave Assisted, Synthesis of Symmetrical Disulfides with Triethylammonium Halochromates, (C2H5)3NH+ [CrO3X]-(X=F, Cl)

Mohammad Kazem Mohammadi, Shahriare Ghammamy, and Mohammad Hossein Farjam

*Abstract*—Triethylammonium fluorochromate (TEAFC) and Triethylammonium chlorochromate (TEACC) are new efficient reagents, which are prepared easily and oxidized thiols to the corresponding disulfides swiftly. The reactions perform cleanly and terminate simultaneously at the disulfide stage without any side products. Oxidizing of some thiols to their corresponding disulfides was studied in solution at room temperature and under microwave radiation. The easy procedure, simple work-up, short reaction times, and excellent yields are advantages of these reagents.

*Index terms*—Disulfide, Microwave, Oxidation, Thiol, Triethylammonium Halochromates.

## I. INTRODUCTION

Oxidative coupling of thiols to disulfides is an important process in organic chemistry and biochemistry, which has been extensively investigated over the years. Disulfide bond formation is important in peptides and bioactive molecules. Disulfides are also key intermediates in a wide variety of organic synthetic processes. Sweetening of catalyst poisons thiols to low volatile disulfides in oil industries and also industrial applications of disulfides in vulcanization of rubbers and elastomers led us to investigate the introduction and applications of new member of this category of reagents in oxidation of thiols to the corresponding disulfides. This conversion has been accomplished using reagents such as molecular oxygen, [1] metal ions, [2] Bu3SnOMe/FeCl3, [3]nitric oxide,[4] halogens, [5-7] sodium perborate, [8]borohydride exchange resin (BER)-transition metal salt system, [9] a morpholine iodine complex, [10] pyridinium chlorochromate (PCC),[11] ammonium persulfate, [12] / CuSO4, [13] and KMnO4 Tributylammonium Halochromates [14]. There are some disadvantages in these reagents such as availability of the reagent, cumbersome procedure, high cost of the reagent, over oxidation or oxidation of other functional groups presented in thiols. Synthesize disulfides from the corresponding thiols under mild reaction conditions using new efficient reagent is desirable. These reactions are interested from an ecological viewpoint, high yield, selectivity and simplicity of the reaction procedure. Triethylammonium fluorochromate and Triethylammonium chlorochromate (TEAFC and TEACC) simplifies oxidizing of the thiols to their disulfides efficiently under better reaction conditions.

### II. EXPERIMENTAL

CrO<sub>3</sub> (Merck, P.A.) was used without further purification. Solvents were purified by standard methods. Infrared spectra were recorded as KBr disks on a Shimadzu model 420 spectrophotometer. The UV/Visible measurements were made on an Uvicon model 922 spectrometer. <sup>1</sup>H and <sup>13</sup>C (for TEAFC and TEACC) were carried out on a Bruker AVANCE DRX 500 spectrometer at 500, 125, 470.66 MHz. All the chemical shifts are quoted in ppm using the high-frequency positive convention; <sup>1</sup>H and <sup>13</sup>C NMR spectra were referenced to external SiMe<sub>4</sub>. Chromium was estimated iodometrically. In the case of the reduced product of the oxidant, chromium was determined after oxidizing with acidic peroxodisulfate (K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>) solution. The relative concentrations of carbon, hydrogen and nitrogen were obtained from the microanalytical laboratories, Department of Chemistry, OIRC, Tehran. Melting points were measured on an Electrothermal 9100 melting point apparatus. A microsynth milstone laboratory microwave oven has been used

## *A.* Synthesis of Triethylammonium Fluorochromate (TEAFC), (C2H5)3NH+[CrO3F]-

A 10g (100 mmol) sample of chromium (VI) oxide, CrO<sub>3</sub>, and 9ml (200 mmol) of 40% hydrofluoric acid were added to 20 ml of water in a 100 ml polyethylene beaker with stirring. After 5-7 min the homogeneous solution was cooled to ca. 0-2 °C. To the resultant clear orange solution, triethylamine (14ml, 100 mmol) was added dropwise with stirring to this solution over a period of 0.5 h and stirring was continued for 0.5 h at -4 °C. The precipitated yellowish-orange solid was isolated by filtration on a polyethylene funnel, washed with petroleum ether  $(3 \times 60 \text{ ml})$  and dried in vacuum for 2 h at room temperature. Yield: 19.44 g (88%); mp 132 °C. C<sub>6</sub>H<sub>16</sub>CrFNO<sub>3</sub>: Calc. C, 32.57; H, 7.23; N, 6.33 Found: C, 32.08; H, 7.64; N, 6.44. I.R. (KBr): 904 cm<sup>-1</sup> v<sub>1</sub>(A<sub>1</sub>) or  $v(CrO_3)$ , 648 cm<sup>-1</sup> v <sub>2</sub>(A<sub>1</sub>) or v(Cr-F), 948 cm<sup>-1</sup> v<sub>4</sub>(E) or v(CrO<sub>3</sub>) cm<sup>-1</sup>. UV/Visible, <sup>13</sup>C NMR and <sup>1</sup>H NMR were all consistent with the TEAFC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of 0.01 M solution of TEAFC in water was 3.45. (Scheme 2)

## *B.* Synthesis of Triethylammonium Chlorochromate (TEACC), (C2H5)3NH+[CrO3Cl]-

Chromium (VI) oxide (10.0 g, 100 mmol) was dissolved in water in a beaker and hydrochloric acid (2.51 ml, 150 mmol) was added with stirring at 0 °C. To the resultant clear orange

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Mohammad Kazem Mohammadi is with Faculty of Science, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran.mohammadi@iauahvaz.ac.ir

Shahriare Ghammamy is with Department of Chemistry, Faculty of Science, Imam Khomeini International University, Qazvin, Iran, postal code:288

Mohammad Hossein Farjam is with Department of Chemistry, Firoozabad Branch, slamic Azad University, Firoozabad, Iran

solution, triethylamine (14ml, 100 mmol) was added drop wise with stirring to this 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 ether (3 × 60 ml) and dried in vacuum for 2 h at room temperature. Yield: 12.82 g (54%); mp 120 °C. C<sub>6</sub>H<sub>16</sub>ClCrNO<sub>3</sub>: Calc. C, 30.31; H, 6.73; N, 5.89 Found: C, 30.29; H, 6.81; N, 5.82. I.R. (KBr): 900 cm<sup>-1</sup> v<sub>1</sub>(A<sub>1</sub>) or v(CrO<sub>3</sub>), 434 cm<sup>-1</sup> v <sub>2</sub>(A<sub>1</sub>) or v(Cr-Cl), 950 cm<sup>-1</sup> v<sub>4</sub>(E) or v(CrO<sub>3</sub>) cm<sup>-1</sup>. UV/Visible, <sup>13</sup>C NMR and 1H NMR were all consistent with the TEACC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of 0.01 M solution of TEACC in water was 2.4. (scheme2)



Scheme 2

# *C. General procedure for oxidative coupling of thiols in dichloromethane*

To a stirred Solution of 4-methylthiophenol (0.248 g, 2 mmol) in 5 ml of dichloromethane, 1 mmol of TEAFC or TEACC was added, and the mixture was stirred at room temperature for the time indicated in the Table 1,2. A solid was formed and was treated with a 1:1 mixture of ether and water (2 ml). The reaction mixture was extracted with ether  $(3 \times 10 \text{ ml})$ . The organic layers were combined together and dried over anhydrous MgSO<sub>4</sub>. Evaporation of the solvent followed by recrystallization or chromatography on silica gel afforded the pure disulfides in the yield indicated in the table, which characterized from its NMR and IR spectrum mp 45°C (Lit. [15]mp 45-46 °C).

## *D. General procedure for oxidative coupling of thiols under microwave irradiations*

To a stirred suspension of Triethylammonium halochromate, (1mmol) in dichloromethane (generally 5 ml), a solution of the substrate in the minimum amount of dichloromethane was added drop wise, the molar ratio of substrate to the oxidant being 1:2. The mixture was irradiated for the time indicated in the table by microwave radiation. The completion of the reaction is followed by UV/Visible and TLC using ether/petroleum ether (60/40) as eluant. The mixture was diluted with ether (1:1 vol/vol) and filtered through a short column of silica gel to give a clear solution.

The solution was evaporated and the residual product purified by distillation, recrystallization or column chromatography. The progress of the reactions was also monitored and checked by UV/Visible spectrophotometry. The amount of the oxidant during the reaction was measured spectrophotometrically at 348 nm and 355 nm for TEAFC and TEACC respectively. A very small magnetic stirrer was designed at the cell (10 mm quartz cell) compartment just in the bottom of sample cell in the spectrophotometer to stir up the solution under study in cell. The reaction mixtures remained homogenous in the solvent system used. The characteristic data for all new products are similar to same compounds that produced from other methods. [16]

### III. RESULTS AND DISCUSSION

The oxidative couplings of thiols by TEAFC and TEACC were investigated in dichloromethane at room temperature and under microwave radiation. As it is shown in table 1 and 2, a series of aliphatic and aromatic thiols were reacted with the reagents with a mole ratio of 2/1 and the corresponding disulfides were obtained with excellent yields. These oxidations were also performed under microwave radiation with the same mole ratios. The results show that under microwave radiation, the reactions are faster.

The practical choice is oriented by the solubility of the products and the desired reaction temperature. The chromium (VI) contents easily determined iodometrically. It seemed from the table 1 that TEAFC were more effective than TEACC for saturated organic thiols (1-8) especially in time of the reaction. This is probably according to higher electro negativity of fluore atom in TEAFC than TEACC. [18]

As may be seen, the method offers a simple, mild, and efficient solid state route for the oxidation of a variety of thiols to the corresponding disulfides. Notably, disulfides did not undergo further oxidation to their corresponding disulfide S-oxides (thiolsulfinates), disulfide S-dioxides (thiolsulfonates), and/or sulfonic acids under the reaction conditions. It must also be noted that no severe exothermal or other safety problems were observed during the mixing of the starting materials and the reactions themselves.

Thus, the said oxidative method under mild conditions has set out to minimize the dispersion of offensive materials in the environment and maximize the use of renewable resources. From this standpoint this method can be considered as a relatively green technology having more advantages and wider applicability compared to the conventional oxidative reagents. (See table 1 and 2)

TABLE 1. OXIDATIVE COUPLING OF THIOLS WITH TRIEAFC IN SOLUTION AND MICROWAVE RADIATION





TABLE 2. OXIDATIVE COUPLING OF THIOLS WITH TRIEACC IN SOLUTION AND MICROWAVE RADIATION						
		Solution			Solution under Microwave	
	Substrate	Time (min)	Product	Yield (%)	Time (min)	Yield (%)
1	S H	150	s s	74	12	92
2	H <sub>4</sub> s-H	110	A s s a	75	10	87
3	H <sub>7</sub> s <sup>H</sup>	95	H7 s H7	70	9	85
4	S—н	145	s—s—	67	14	89
5	O S H	210		75	25	90
6	S—н	50	s—s—s	70	4	85



The yields of the products are, in general, good. In some cases, lower yields were obtained as the loss of the products could not be avoided during the isolation process due to highly volatile nature of the products. Sometimes the products were contaminated (as detected by 1H NMR) with starting materials after initial isolation, which were further purified by filtration chromatography over a short plug of silica gel or neutral silica using hexane as eluent. Some unidentified by-products were formed (to the extent of nearly 10% by 1H NMR) in a few cases which were removed by column chromatography. It is important to emphasize that the reactions could be terminated simultaneously at the disulfide stage. (See table 1, 2)

Over-oxidation has not been observed, even though the reactions were carried out various conditions. (Scheme 1.)



Scheme1

### IV. CONCLUSIONS

In conclusion, we described a highly efficient microwaveinduced modification of conventional heating procedure for the oxidation of thiols that allows for the rapid synthesis of disulfides. The advantages of this environmentally benign and safe protocol, included a simple reaction set-up, application of commercially available quaternary ammonium salts and catalysts, high product yields, short reaction time as well as the elimination of side products.

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**Mohammad Kazem Mohammadi**, photograph and biography not available at the time of publishing.

Shahriare Ghammamy, photograph and biography not available at the time of publishing.

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