

## Triethylammonium Halochromates, $(C_2H_5)_3NH^+ [CrO_3X]^-$ (X=F, Cl), Reagents for Efficient Oxidation Coupling of Thiols to Disulfides

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**Abstract.** Triethylammonium fluorochromate (TriE AFC) and Triethylammonium chlorochromate (TriE ACC) 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.

**Key words:** Thiol, Oxidation, Disulfide, Triethylammonium Fluorochromate, Triethylammonium Chlorochromate, Solution, Microwave

### 1. 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. This conversion has been accomplished using reagents such as molecular oxygen,<sup>1</sup> metal ions,<sup>2</sup> Bu<sub>3</sub>SnOMe/FeCl<sub>3</sub>,<sup>3</sup> nitric oxide,<sup>4</sup> halogens,<sup>5-8</sup> sodium perborate,<sup>9</sup> borohydride exchange resin (BER)-transition metal salt system,<sup>10</sup> a morpholine iodine complex,<sup>11</sup> pyridinium chlorochromate (PCC),<sup>12</sup> ammonium persulfate,<sup>13</sup> KMnO<sub>4</sub>/CuSO<sub>4</sub>,<sup>14</sup>. 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 (TriE AFC and TriE ACC) simplifies oxidizing of the thiols to their disulfides efficiently under better reaction conditions.

### 2. Results and discussion

The oxidative couplings of thiols by TriE AFC and TriE ACC 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.

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 TriE AFC in solution and microwave radiation

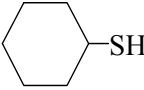
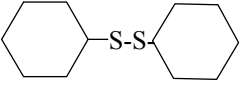
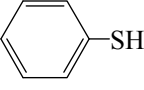
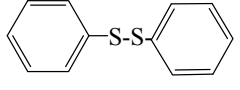
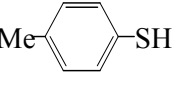
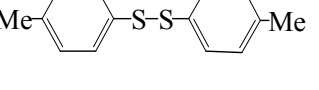
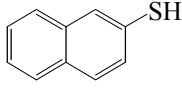
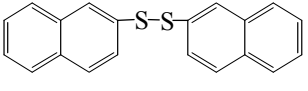
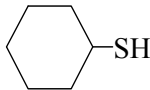
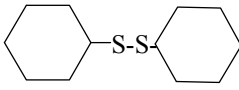
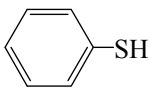
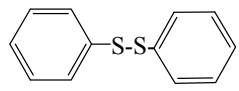
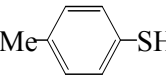
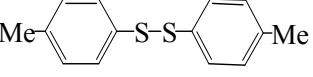
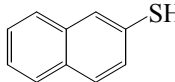
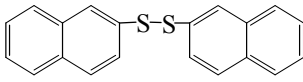
Substrate	Solution			Solution under Microwave	
	Time (min)	Product	Yield (%)	Time (min)	Yield (%)
1 $\text{CH}_3\text{-CH(SH)-CH}_3$	60	$\text{CH}_3\text{-CH(S-S-CH)-CH}_3$	78	6	85
2 $\text{n-C}_5\text{H}_{11}\text{-SH}$	58	$\text{C}_5\text{H}_{11}\text{-S-S-C}_5\text{H}_{11}$	86	6	89
3 $\text{n-C}_8\text{H}_{17}\text{-SH}$	60	$\text{C}_8\text{H}_{17}\text{-S-S-C}_8\text{H}_{17}$	78	6	92
4 	55		35	8	89
5 $\text{HOOC-CH}_2\text{-SH}$	58	$\text{HOOC-CH}_2\text{-S-S-H}_2\text{COOH}$	75	6	95
6 	65		72	10	87
7 	70		70	8	84
8 	75		64	12	81

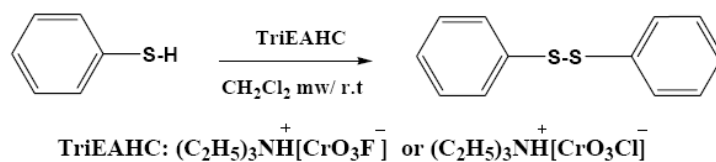
Table 2. Oxidative coupling of thiols with TriE ACC in solution and microwave radiation

Substrate	Solution			Solution under Microwave	
	Time (min)	Product	Yield (%)	Time (min)	Yield (%)
1 $\text{CH}_3\text{-CH(SH)-CH}_3$	150	$\text{CH}_3\text{-CH(S-S-CH)-CH}_3$	74	12	92
2 $\text{n-C}_5\text{H}_{11}\text{-SH}$	110	$\text{C}_5\text{H}_{11}\text{-S-S-C}_5\text{H}_{11}$	75	10	87
3 $\text{n-C}_8\text{H}_{17}\text{-SH}$	95	$\text{C}_8\text{H}_{17}\text{-S-S-C}_8\text{H}_{17}$	70	9	85

4		145		67	14	89
5	HOOC-CH <sub>2</sub> -SH	210	HOOC-CH <sub>2</sub> -S-S-H <sub>2</sub> COOH	75	25	90
6		50		70	4	85
7		40		69	4	90
8		55		63	8	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 <sup>1</sup>H 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 <sup>1</sup>H 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

### 3. 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. Proton, <sup>13</sup>C, <sup>19</sup>F NMR (for TriEAFC) 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> and <sup>19</sup>F NMR spectra to external CFCl<sub>3</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.

#### 3.1. Synthesis of Triethylammonium Fluorochromate (TriEAFC), (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>NH<sup>+</sup> [CrO<sub>3</sub>F<sup>-</sup>]

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 × 60 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> ν<sub>1</sub>(A<sub>1</sub>) or ν(CrO<sub>3</sub>), 648 cm<sup>-1</sup> ν<sub>2</sub>(A<sub>1</sub>) or ν(Cr-F), 948 cm<sup>-1</sup> ν<sub>4</sub>(E) or ν(CrO<sub>3</sub>) cm<sup>-1</sup>. UV/Visible, <sup>13</sup>C NMR, <sup>1</sup>H NMR and <sup>19</sup>F NMR were all consistent with the TriEAFC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of 0.01 M solution of TriEAFC in water was 3.45.

### 3.2. Synthesis of Triethylammonium Chlorochromate (TriEACC), (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>NH<sup>+</sup> [CrO<sub>3</sub>Cl]<sup>-</sup>

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 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> ν<sub>1</sub>(A<sub>1</sub>) or ν(CrO<sub>3</sub>), 434 cm<sup>-1</sup> ν<sub>2</sub>(A<sub>1</sub>) or ν(Cr-Cl), 950 cm<sup>-1</sup> ν<sub>4</sub>(E) or ν(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 TriEACC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of 0.01 M solution of TriEACC in water was 2.4.

### 3.3. 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 TriEAFC or TriEACC was added, and the mixture was stirred at room temperature for the time indicated in the Table. 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 × 10 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.<sup>15</sup> mp 45-46 °C).

### 3.4. 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 TriEAFC and TriEACC 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.

## 4. Acknowledgements

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## 5. References

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