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Efficient oxidation of thiols to disulfides by triethylammonium halochromates $(C_2H_5)_3NH^+[CrO_3X]^-$, (X=F, Cl) under microwave irradiation

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ABSTRACT

Triethylammonium fluorochromate (TEAFC) and Triethylammonium chlorochromate (TEACC) are new efficient reagents, which were easily prepared 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, were advantages of these reagents.

KEYWORDS

Triethylammonium
Halochromates;
Thiol;
Oxidation;
Disulfide;
Microwave irradiation.

INTRODUCTION

Oxidative coupling of thiols to disulfides was an important process in organic chemistry and biochemistry, which was extensively investigated over the years. Disulfide bond formation was important in peptides and bioactive molecules. This conversion was accomplished using reagents such as molecular oxygen[1], metal ions[2], $Bu_3SnOMe/FeCl_3$[3], nitric oxide[4], halogens[5-8], sodium perborate[9], borohydride exchange resin (BER)-transition metal salt system[10], morpholine iodine complex[11], pyridinium chlorochromate (PCC)[12], ammonium persulfate[13] and $KMnO_4/CuSO_4$[14]. There were 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. Synthesized disulfides from the corresponding thiols under mild reaction conditions using new efficient reagent were desirable. These reactions were interested from an ecological viewpoint, high yield, selectivity and simplicity of the reaction procedure. In constitution to our interest to developing oxidative process[15,16], we synthesized Triethylammonium fluorochromate (TEAFC) and Triethylammonium chlorochromate (TEACC) simplifies oxidizing of the thiols to their disulfides efficiently in room temperature and microwave irradiation.

EXPRIMENTAL

Material and methods

CrO_3 (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. ^1H and ^{13}C NMR (for TEAFC) 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; ^1H and ^{13}C NMR spectra were referenced to external $SiMe_4$. Chromium was estimated iodometrically. In the case of the reduced product of the oxidant, chromium was determined after oxidizing with acidic peroxodisulfate ($K_2S_2O_8$) 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. Experiments were carried out in closed vessel multi mode Microsynth Milstone laboratory microwave oven using a 900 Watts Westpointe microwave operating at 3.67 GHz. All experiments had good reproducibility by repeat the experiments in same conditions.

Synthesis of triethylammonium fluorochromate (TEAFC), $(C_2H_5)_3NH^+ [CrO_3F]^-$

A 10g (100 mmol) sample of chromium (VI) oxide, CrO_3, 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%); m.p. 132 °C. $C_6H_{16}CrFNO_3$: Calc. C, 32.57; H, 7.23; N, 6.33 Found: C, 32.08; H, 7.64; N, 6.44. IR (KBr): 904 cm^{-1} $\nu_1(A_1)$ or $\nu(CrO_3)$, 648 cm^{-1} $\nu_2(A_1)$ or ν(Cr-F), 948 cm^{-1} $\nu_4(E)$ or $\nu(CrO_3)$ cm^{-1}. UV/Visible, ^{13}C NMR and ^1H NMR were all consistent with the TEAFC structure. The above procedure could be scaled up to larger quantities, if desired. The pH of 0.01 M solution of TEAFC in water was 3.45.

Synthesis of triethylammonium chlorochromate (TEACC),$(C_2H_5)_3NH^+ [CrO_3Cl]^-$

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%); m.p. 120 °C. $C_6H_{16}ClCrNO_3$: Calc. C, 30.31; H, 6.73; N, 5.89 Found: C, 30.29; H, 6.81; N, 5.82. IR (KBr): 900 cm^{-1} $\nu_1(A_1)$ or $\nu(CrO_3)$, 434 cm^{-1} $\nu_2(A_1)$ or ν(Cr-Cl), 950 cm^{-1} $\nu_4(E)$ or $\nu(CrO_3)$ cm^{-1}. UV/Visible, ^{13}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.

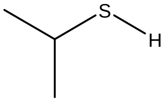
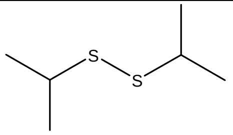
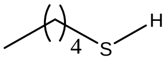
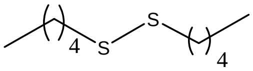
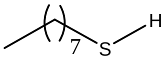
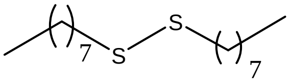
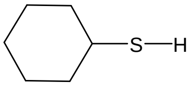
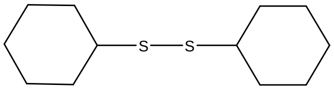
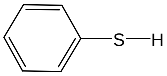
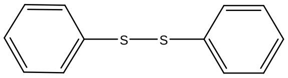
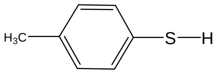
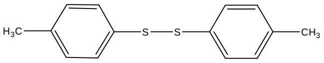
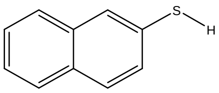
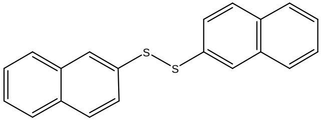
General procedure for oxidative coupling of thiols to disulfides in room temprature

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. 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 $MgSO_4$. Evaporation of the solvent followed by recrystallization or chromatography on silica gel afforded the pure disulfides in the yield indicated in the TABLE 1, which characterized from its NMR and IR spectrum mp 45°C (Lit[17].mp 45-46 °C).

General procedure for oxidative coupling of thiols to disulfides in microwave radiation

To a stirred suspension of Triethylammonium halochromates, (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.

TABLE 1 : Oxidative coupling of thiols with TEAFC in solution and microwave radiation

	Substrate	Solution			Solution under Microwave	
		Time (min)	Product	Yield (%)	Time (min)	Yield (%)
1	 1a	60	 2a	78	6	85
2	 1b	58	 2b	86	11	89
3	 1c	60	 2c	78	13	92
4	 1d	55	 2d	35	8	89
5	HOOC-CH$_2$-SH 1e	58	HOOC-CH$_2$-S-S-H$_2$COOH 2e	75	6	95
6	 1f	65	 2f	72	10	87
7	 1g	70	 2g	70	8	84
8	 1h	75	 2h	64	12	81

Spectral data for disulfides

1,2 - diisopropyldisulfane (2a, 4a). IR (KBr) cm $^{-1}$ 3000-2900 C-H (aliph. strech), 1400-1350 C-H (aliph.bend), 1200- 1100 C-S (strech). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.7 (m, 2H),1.5 (d, 12H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 38.5 (d), 24(q). HRMS Calcd for $C_6H_{14}S_2$: M$^+$, 150.4125. Found : *m/z* 150.4117(average). oil[18]

1,2- dipentyldisulfane (2b, 4b). IR (KBr) cm $^{-1}$ 3000-2900 C-H (aliph. strech) 1200- 1100 C-S (strech). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.5 (t, 4 H),1.6 (m, 4H), 1.25(m, 4H) 1.3 (m, 4H),.85 (t, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36, 33, 31, 23.5, 14.5. HRMS Calcd for $C_{10}H_{22}S_2$: M$^+$, 206.8542. Found: *m/z* 206.1654(average). oil[18]

1,2 – dioctyldisulfane (2c, 4c).IR (KBr) cm $^{-1}$ 3000-2900 C-H (aliph. strech) 1200- 1100 C-S (strech). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.6 (t, 4 H),1.5 (m, 4H), 1.2(m, 18H).9 (t, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.66, 32.5, 31.43, 31.35, 31.22, 27.03, 23.5, 15.02. HRMS Calcd for $C_{16}H_{34}S_2$: M $^+$, 290.1213. Found : *m/z* 290.3564(average). oil [18].

1,2 dicyclohexyl disulfane (2d, 4d). IR (KBr) cm $^{-1}$ 3000-2900 C-H (aliph. strech), 1200- 1100 C-S (strech). ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.5 (m, 2 H),1.65 (dt, 8H), 1.4 (m, 12H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 52.56, 34.52, 26.59, 25.38. HRMS Calcd for $C_{12}H_{22}S_2$: M$^+$, 230.2135. Found: *m/z* 230.2120 (average). oil[18]

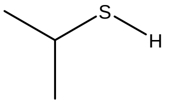
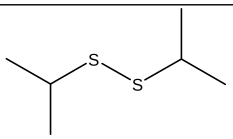
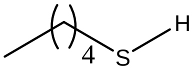
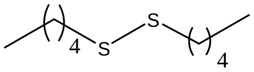
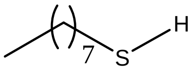
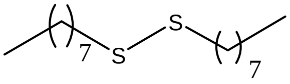
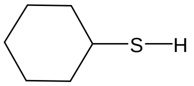
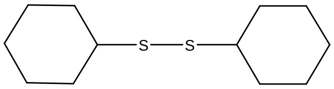
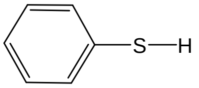
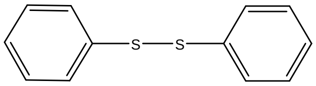
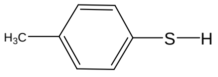
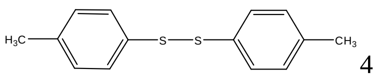
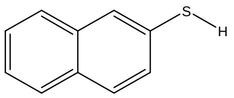
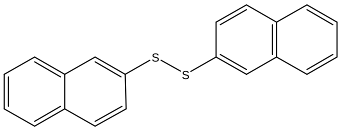
disulfanyl –acetic acid (2e, 4e). IR (KBr) cm $^{-1}$ 3500-3200 COOH (strech), 3000-2900 C-H (aliph. strech),1200- 1100 C-S (strech). ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.27 (s, 4H),11.5 (s, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 35 (t), 179 (s). HRMS Calcd for $C_4H_6O_4S_2$: M$^+$, 182.1478, Found: *m/z* 182.342(1average). oil[18]

1,2 diphenyldisulfane (2f, 4f). IR (KBr) cm $^{-1}$ 3200-3100 C-H (Ar. strech), 1200- 1150 C-S (strech). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.65 (d, 4 H),7.25 (m, 6H). ^{13}C NMR (125MHz, CDCl$_3$) δ 133, 131.4, 130.2, 129.53. $C_{12}H_{10}S_2$: Calc. C, 66.1; H, 4.71; S, 29.37. Found: C, 66.22; H, 4.65; S, 29.2. m.p. 57-58 ^{0}C, lit[19] 58-60 ^{0}C.

1,2-di-p- tolyldisulfane or bis (4-methylphenyl)disulfide (2g, 4g). IR (KBr) cm $^{-1}$ 3200-2100 C-H (Ar. strech), 3000-2900 C-H (aliph. strech) 1480-1400 C-H (Ar.bend),1200- 1100 C-S (strech). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.5 (d, 4 H), 7.2(d, 4H), 2.5(s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 126 (S), 130 (d), 127 (d), 124 (s), 21 (q).$C_{14}H_{14}S_2$: Calc. C,68.29; H, 5.70; S, 26.1. Found: C, 68.46; H, 5.60; S, 26.23. m.p.42- 44^{0}C, lit[19] 43-44^{0}C.

1- (n- naphthalene – 3 – yl) -2- (naphthalene – 6- yl) disulfane (2h, 4h). IR (KBr) cm $^{-1}$ 3200-3100 C-H (Ar. strech), 1200- 1150 C-S (strech). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.1 (s, 2 H),7.7 (d, 2H), 7.5

TABLE 2 : Oxidative coupling of thiols with TEACC in solution and microwave radiation

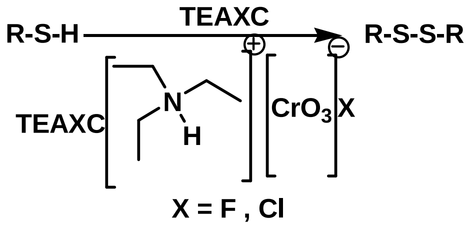
	Substrate	Solution			Solution under Microwave	
		Time (min)	Product	Yield (%)	Time (min)	Yield (%)
1	 3a	150	 4a	74	12	92
2	 3b	110	 4b	75	10	87
3	 3c	95	 4c	70	9	85
4	 3d	145	 4d	67	14	89
5	HOOC-CH$_2$-SH 3e	210	HOOC-CH$_2$-S-S-H$_2$COOH 4e	75	25	90
6	 3f	50	 4f	70	6	85
7	 3g	40	 4g	69	4	90
8	 3h	55	 4g	63	8	85

(d,6H) 7.32(d,4H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.76, 137.11, 135.26, 134.52, 131.57, 128.92, 127.08, 126.16, 125.02, 124.87. $C_{20}H_{14}S_2$: Calc. C,75.47; H, 4.40; S, 20.12. Found: C, 75.36; H, 4.32; S, 20.89. m.p 140-142 ^{0}C. lit.[19] 142- 145 ^{0}C.

RESULTS AND DISSCUSSIONS

The oxidative couplings of thiols by TEAFC and TEACC were investigated in dichloromethane at room temperature and under microwave radiation. As it was shown in TABLE 1 and 2, a series of aliphatic and aromatic thiols were reacted with the reagents with a mole ratio of 1/1 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 were faster.

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



Scheme 1

The yields of the products were, 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 ^{1}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 5% by ^{1}H NMR) in a few cases which were removed by column chromatography. It was important to emphasize that the reactions could be terminated simultaneously at the disulfide stage. (TABLE 1, 2)

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

CONCLUSION

The present procedure using Triethylammonium halochromates (TEAXC) in solvent and microwave conditions has been found to oxidize selectively primary aliphatic, aromatic and allylic thiols to corresponding disulphides without isomerization and polymerization of double bonds, over oxidation and other side-reactions keeping intact the acid sensitive functionalities, (scheme 2). The important advantages of this procedure include (a) operational simplicity (ease of set up and work-up), (b) good yield of the oxidized products, with high purity (by immobilization of the chromium by-products on the surface of silica), (c) mild reaction conditions, (d) good selectivity and (e) general applicability accommodating a variety of substitution patterns.

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