



Triethylammonium halochromates, $(C_2H_5)_3NH^+[CrO_3X]^-$ (X=F, Cl), reagents for efficient oxidation coupling of thiols to disulfides

Mohammad Kazem Mohammadi

College of Sciences, Ahvaz Branch, Islamic Azad University, Ahvaz, (IRAN)

E-mail: mkmohamadi@yahoo.com

ABSTRACT

Triethylammonium fluorochromate (TriEAFC) and Triethylammonium chlorochromate (TriEACC) 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. The easy procedure, simple work-up, short reaction times, and excellent yields are advantages of these reagents. © 2014 Trade Science Inc. - INDIA

KEYWORDS

Thiol;
Oxidation;
Disulfide;
Triethylammonium
fluorochromate;
Triethylammonium
chlorochromate.

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^[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], a morpholine iodine complex^[11], pyridinium chlorochromate (PCC)^[12], ammonium persulfate^[13], $KMnO_4/CuSO_4$ ^[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 pro-

cedure. Triethylammonium fluorochromate and Triethylammonium chlorochromate (TriEAFC and TriEACC) simplifies oxidizing of the thiols to their disulfides efficiently under better reaction conditions.

EXPERIMENTAL

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. The UV/Visible measurements were made on an Uvicon model 922 spectrometer. Proton, ^{13}C , ^{19}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; 1H and ^{13}C NMR spectra were referenced to external $SiMe_4$ and ^{19}F NMR spectra to external $CFCl_3$. Chromium was estimated iodometrically. In the case of the reduced product of the oxidant, chromium was determined after oxidizing with acidic

Full Paper

peroxodisulfate (K₂S₂O₈) 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.

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

A 10g (100 mmol) sample of chromium (VI) oxide, CrO₃, 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. C₆H₁₆CrFNO₃: 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⁻¹ ν₁(A₁) or ν(CrO₃), 648 cm⁻¹ ν₂(A₁) or ν(Cr-F), 948 cm⁻¹ ν₄(E) or ν(CrO₃) cm⁻¹. UV/Visible, ¹³C NMR, ¹H NMR and ¹⁹F NMR were all consistent with the TriE AFC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of 0.01 M solution of TriE AFC in water was 3.45.

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

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%); mp 120 °C. C₆H₁₆ClCrNO₃: 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⁻¹ ν₁(A₁) or ν(CrO₃), 434 cm⁻¹ ν₂(A₁) or ν(Cr-Cl), 950 cm⁻¹ ν₄(E) or ν(CrO₃) cm⁻¹. UV/Visible, ¹³C NMR and ¹H NMR were all consistent with the TriE ACC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of 0.01 M solution of TriE ACC in water was 2.4.

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 TriE AFC or TriE ACC 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 MgSO₄. 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.¹⁵mp 45-46 °C).

RESULTS AND DISCUSSION

The oxidative couplings of thiols by TriE AFC and TriE ACC were investigated in dichloromethane at room temperature. 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.

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)

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 de-

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

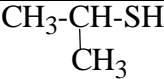
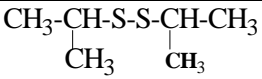
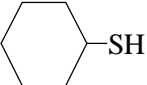
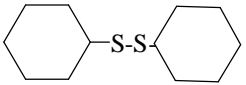
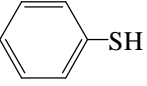
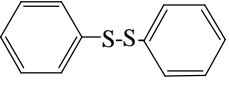
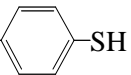
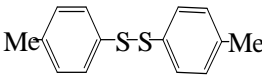
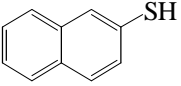
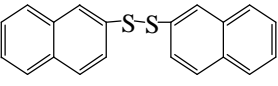
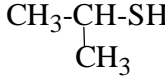
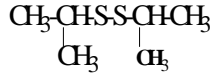
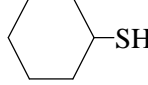
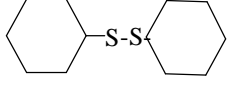
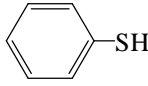
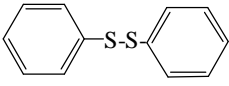
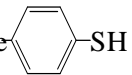
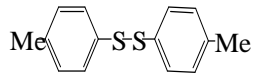
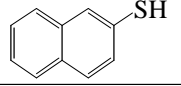
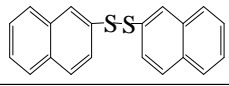
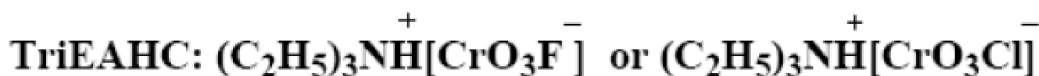
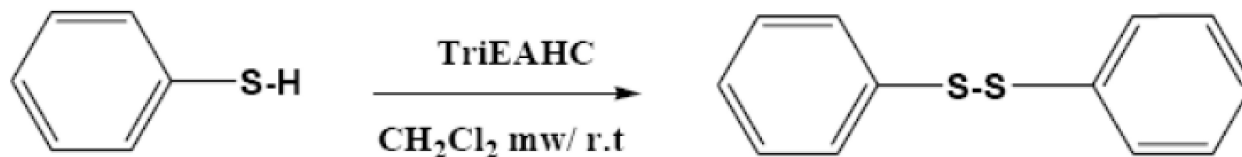
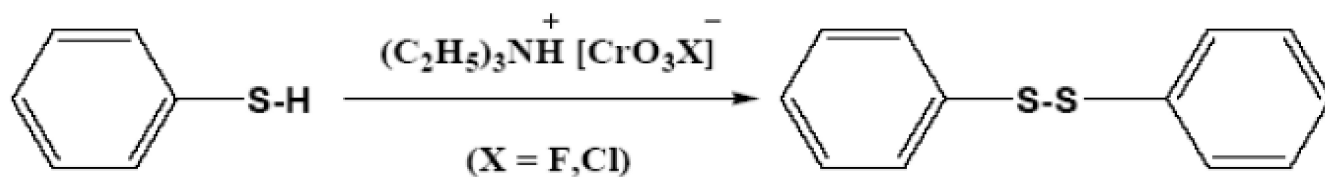
Substrate	Solution		
	Time (min)	Product	Yield (%)
1 	60		78
2 n-C ₅ H ₁₁ -SH	58	C ₅ H ₁₁ -S-S-C ₅ H ₁₁	86
3 n-C ₈ H ₁₇ -SH	60	C ₈ H ₁₇ -S-S-C ₈ H ₁₇	78
4 	55		35
5 HOOC-CH ₂ -SH	58	HOOC-CH ₂ -S-S-H ₂ COOH	75
6 	65		72
7 Me- 	70	Me- 	70
8 	75		64

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

Substrate	Solution		
	Time (min)	Product	Yield (%)
1 	150		74
2 n-C ₅ H ₁₁ -SH	110	C ₅ H ₁₁ -S-S-C ₅ H ₁₁	75
3 n-C ₈ H ₁₇ -SH	95	C ₈ H ₁₇ -S-S-C ₈ H ₁₇	70
4 	145		67
5 HOOC-CH ₂ -SH	210	HOOC-CH ₂ -S-S-H ₂ COOH	75
6 	50		70
7 Me- 	40	Me- 	69
8 	55		63



Scheme 1



Scheme 2

tected 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.)

CONCLUSIONS

The present procedure using Triethylammonium Chlorochromate (TriEACC), $(\text{C}_2\text{H}_5)_3\text{NH}^+[\text{CrO}_3\text{Cl}]^-$ 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 sim-

Full Paper

plicity (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.

ACKNOWLEDGEMENTS

This work is financially supported by the research council of Imam Khomeini International University.

REFERENCES

- [1] K.T.Liu, Y.C.Tong; *Synthesis*, 669–670 (1978).
- [2] T.J.Wallace; *J.Org.Chem.*, **31**, 3071–3079 (1966).
- [3] T.Sato, J.Otera, H.Nozaiki; *Tetrahedron Lett.*, **31**, 3591–3594 (1990).
- [4] W.A.Pryor, D.F.Church, C.K.Govindan, G.Crank; *J.Org.Chem.*, **47**, 156–159 (1982).
- [5] J.R.Schaeffer, C.D.Goodhue, H.A.Risle, R.E.Stevens; *J.Org.Chem.*, **32**, 392–395 (1967).
- [6] J.Drabowicz, M.Mikolajczyk; *Synthesis*, 32–34 (1980).
- [7] M.H.Ali, M.McDermott; *Tetrahedron Lett.*, **43**, 6271–6273 (2002).
- [8] T.Aida, T.Akasaka, N.Furukawa, S.Oae; *Bull. Chem.Soc.Jpn.*, **49**, 1441–1448 (1976).
- [9] A.McKillop, D.Koyuncu; *Tetrahedron Lett.*, **31**, 5007–5010 (1990).
- [10] J.Choi, N.M.Yoon; *J.Org.Chem.*, **60**, 3266–3267 (1995).
- [11] K.Ramadas, N.Srinivasan; *Synth.Comm.*, **26**, 4179–4184 (1996).
- [12] P.Salehi, A.Farrokh, M.Gholizadeh; *Synth. Commun.*, **31**, 2777–2781 (2001).
- [13] R.S.Varma, H.M.Meshram, R.Dahiya; *Synth. Commun.*, **30**, 1249–1255 (2000).
- [14] N.A.Noureldin, M.Caldwell, J.Hendry, D.G.Lee; *Synthesis*, 1587–1589 (1998).
- [15] N.Iranpoor, B.Zeynizadeh; *Synthesis*, 49-50 (1999).