Bull. Chem. Soc. Ethiop. **2012**, 26(1), 139-144.
Printed in Ethiopia
DOI: http://dx.doi.org/10.4314/bcse.v26i1.16
ISSN 1011-3924

SHORT COMMUNICATION

MICROWAVE ASSISTED OXIDATIVE COUPLING OF THIOLS TO SYMMETRICAL DISULFIDES WITH TRIPROPYLAMMONIUM FLUOROCHROMATE(VI) (TPAFC)

Mohammad Kazem Mohammadi[1*] and Shahriare Ghammamy[2]

[1]Faculty of Science, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran
[2]Department of Chemistry, Faculty of Science, Imam Khomeini International University, Qazvin, Iran

(Received August 3, 2010; revised October 24, 2011)

ABSTRACT. Tripropylammonium fluorochromate(VI) (TPAFC) is an efficient and novel reagent, which can be prepared easily and oxidizes thiols to the corresponding disulfides, quickly. The reactions are performed cleanly and are controlled to stop at the disulfide stage, without over-oxidation or side products. Coupling of thiols to their corresponding disulfides, was studied in solution at room temperature and under conditions using a minimal amount of solvent under microwave irradiation. The easy procedure, simple work-up, short reaction times, and excellent yields are other advantages of this reagent.

KEY WORDS: Thiol, Oxidation, Coupling, Disulfide, Tripropylammonium fluorochromate, Microwave irradiation

INTRODUCTION

Many sulfur-oxidizing reagents have been developed in recent years with some success [1]. Disulfides constitute one of the most important organic sulfur containing classes of compounds possessing an unique exclusive chemistry both in biochemistry [2] and in synthetic organic chemistry [3]. Also, disulfides are key intermediates in a wide variety of organic synthetic routes [4-6]. Sweetening of catalyst poisoning thiols to disulfides of low volatility in the oil industry [7-8] and also the industrial applications of disulfides in the vulcanization of rubbers and elastomers led us to investigate a new reagent for the oxidation of thiols to the corresponding disulfides.

Many stoichiometric reagents like manganese dioxide [9], dichromates [10], halosilane-chromium trioxide [11], diethyl azodicarboxylate [12], nickel peroxide [13], chromium peroxide [14], diaryl telluroxide [15], tetrabutylammonium ceric(IV) nitrate [16], sodium perborate [17], silver trifluoromethane sulphonate [18] and permanganate [19] have been developed for this transformation. These reagents suffer from either one or more of the following disadvantages: 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 and efficient new reagents to synthesize disulfides from the corresponding thiols under mild reaction conditions. These reactions should not only be interesting from an ecological viewpoint, but also should offer considerable synthetic advantages in terms of the yield, selectivity and simplicity of the reaction procedure. Microwave synthesis is a relatively new technique which has been found to provide such advantages for a number of other chemical reactions. Acceleration of organic reactions by microwave irradiation has been noted. Overall, in many cases, microwave techniques have been found to be more effective than a conventionally conducted thermal heating of reactions [20].

*Corresponding author. E-mail: mohammadi@iauahvaz.ac.ir

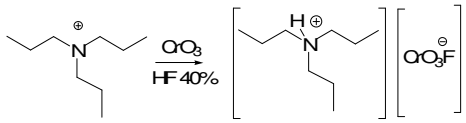
In a number of applications, reactions under microwave conditions have provided pure products in high yield [21]. Against this background**,** we wish to report that tripropylammonium fluorochromate (TPAFC) is able to oxidize thiols to their disulfides efficiently under various reaction conditions. In the following, examples of the oxidative coupling of thiols under solvent-free reactions under microwave irradiation are described. Comparisons with conventional heating methods, realized either in an oil or sand bath at the same temperature used for the microwave experiments will be given where available.

EXPERIMENTAL

Materials and instruments. 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.^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 300 MHz. All the chemical shifts are quoted in ppm using the high-frequency positive convention. ^{1}H and ^{13}C NMR spectra were referenced to external $SiMe_4$. Chromium was analyzed iodometrically. In the case of the reduced product of the oxidant, chromium was determined after oxidation with an acidic peroxodisulfate ($K_2S_2O_8$) solution. The percent composition of carbon, hydrogen and nitrogen were obtained from the micro analytical laboratories, Department of Chemistry, OIRC, Tehran. Melting points were measured on an Electrothermal 9100 melting point apparatus. The authors used a Microsynth Millstone laboratory microwave oven. Experiments were carried out in a closed vessel multi-mode Microsynth Milstone laboratory microwave oven using a 400 Watts Westpoint microwave operating at 3.67 GHz. All experiments had good reproducibility as ascertained by repetition of the experiments under the same conditions.

Preparation of tripropylammonium fluorochromate (TPAFC). A sample of chromium(VI) oxide (CrO_3, 15 g, 150 mmol) and 40% hydrofluoric acid (11.3 mL, 225 mmol) was added to water (20 mL) in a 100 mL polyethylene beaker under stirring. After 5-7 min, the homogeneous solution was cooled to ca. 1-2 °C, and distilled tripropylamine (28.3 mL, 150 mmol) was added in small portions to this solution with stirring over a period of 0.5 h at 0 °C.

The precipitated orange solid was isolated by filtration on a polyethylene funnel, and washed with petroleum ether (3 × 60 mL) and dried *in vacuo* for 2 h at room temperature. Yield: 37.5 g (95%); m.p. 142 °C. $C_9H_{22}CrFNO_3$: calc. C, 41.05; H, 8.35; N, 5.31. Found: C, 41.19; H, 8.43; N, 5.43. IR (KBr): 904 cm^{-1} $\nu_1(A_1)$ or $\nu(CrO_3)$ that shows as ν(Cr-O), 647 cm^{-1} $\nu_2(A_1)$ or ν(Cr-F), 949 cm^{-1} $\nu_4(E)$ or $\nu(CrO_3)$ that shows as ν(Cr-O). Electronic absorption at 248 nm, corresponding to $1a_2 \rightarrow 9e$ (ε = 140 M^{-1} cm^{-1}); 348 nm to $8e \rightarrow 9e$ (ε = 667 M^{-1} cm^{-1}); and 278 nm to $12a_1 \rightarrow 9e$ (ε = 1287 M^{-1} cm^{-1}). ^{1}H-NMR (300 MHz, CD_3CN): δ = 3.23 (*t*, 6 H, 3 CH_2), 1.97 (*m*, 6 H, 3 CH_2), 0.91 (*t*, 9H, CH_3). ^{13}C-NMR (300 MHZ, CD_3CN): δ 11.45, 20.25, 55.26. HRMS Calcd 263.1035 for $C_9H_{22}CrFNO_3$. Found 260.1038. (Scheme 1).

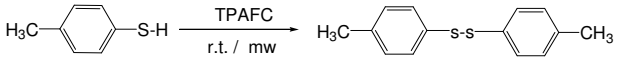


Scheme 1

IR, UV, ^{13}C NMR, and ^{1}H NMR were all consistent with the TPAFC structure. The above procedure can be scaled up to larger quantities, if desired. Molar conductance (Λ_M, 25 °C) of

0.001 M solutions of TPAFC in water was 125 Ω^{-1} cm^2 mol^{-1}. The pH of 0.01 M solution of TPAFC in water was 3.3.

General procedure for the oxidative coupling of thiols in dichloromethane. To a stirred solution of 4-methylthiophenol (0.248 g, 2 mmol) in dichloromethane (5 mL), TPAFC (0.263 g, 1 mmol) was added, and the mixture was stirred at room temperature for 67 min. A solid was formed and 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 and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography (EtOAc/hexane as eluent) afforded the pure disulfide 2 g in 77 % (0.207 g) yield, which was characterized by NMR and IR spectrum. m.p. 45 °C (Lit. [22] m.p. 45-46 °C) (Scheme 2).



Scheme 2

*4,4-Ditolyl disulfide (**2g**).* IR (KBr) cm^{-1} 3200-2100 C-H (Ar . stretch), 3000-2900 C-H (aliph., stretch) 1480-1400 C-H (Ar, bend), 1200-1100 C-S (stretch). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (d, 4 H), 7.2 (d, 4H), 2.5 (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 126.21 (S), 130.42 (d), 127.3 (d), 124.85 (s), 21.17 (q). HRMS calcd 246.05423 for $C_{14}H_{14}S_2$. Found 246.05425.

General procedure for the preparation of silica gel supported TPFAC reagent. A 500 mL suction flask equipped with a constant pressure dropping funnel was used. The cold solution of TPAFC, prepared by completely dissolving of TPAFC (X = F, 0.2 mol, 52.6 g) in CH_2Cl_2 (10 mL), was stirred with silica gel (Aldrich, 150 mesh, 60 g) over a period of 30 min at room temperature. 30 min evaporation of the solvent under high vacuum affords an orange-red slurry of tripropylammonium fluorochromate/silica gel, which is completely dried in 70 ^{o}C for 2 h.

Typical procedure for oxidative coupling of thiophenol with tripropyl ammonium fluorochromate/silica gel under microwave irradiation

*Preparation of diphenyl disulfide (**2f**).* A suspension of thiophenol (**1f**) (0.110 g, 0.001 mol), TPAFC (0.263 g, 0.001 mol) and 1 g wet SiO_2 (50%, w) acetonitrile (2 mL) (for better absorbing the microwave irradiation) was completely mixed and the mixture was irritated in a microwave oven at 2.45 GHz (800 W). The completion of the reaction was followed by TLC using ether/petroleum ether (V:V = 60:40) as eluent. After completion, the mixture was stirred in a EtOH/$CHCl_3$ (V:V = 1:3) solution for separating products from the solid support. This mixture was allowed to stand for 1 h and then filtered, to give a clear solution. The solvent was evaporated and the residual product purified by column chromatography (EtOAc/hexane as eluent) to give diphenyl disulfide (**2f**) in 92% yield in 8 min, m.p. 57-58 ^{o}C (Lit. [23] 58-60 ^{o}C) (Scheme 2).

The above procedure could be carried out in larger scale, without any problems.

Characteristic data for disulfides

*Diisopropyl disulfide (**2a**).* IR (KBr) cm^{-1} 3000-2900 C-H (aliph., stretch), 1400-1350 C-H (aliph., bend), 1200-1100 C-S (stretch). ^{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), 24.65 (q). HRMS calcd 150.0571 for $C_6H_{14}S_2$. Found 150.0569.

*Di-n-pentyl disulfide (**2b**)*. IR (KBr) cm^{-1} 3000-2900 C-H (aliph., stretch), 1200-1100 C-S (stretch). ^1H NMR (300 MHz, $CDCl_3$) δ 2.5 (t, 4 H), 1.6 (m, 4H), 1.25 (m, 4H), 1.3 (m, 4H), 1.2 (t, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 36.53, 33.78, 31.13, 23.55, 14.50. HRMS calcd 206.1281 for $C_{10}H_{22}S_2$. Found 206.1283.

Di-n-octyl disulfide **(2c)**. IR (KBr) cm^{-1} 3000-2900 C-H (aliph., stretch), 1200-1100 C-S (stretch). ^1H NMR (300 MHz, $CDCl_3$) δ 2.6 (t, 4 H), 1.5 (m, 4H), 1.3 (m, 18H) **1.2** (t, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 33.66, 32.5, 31.43, 31.35, 31.22, 27.03, 23.5, 15.02. HRMS calcd 290.2142 for $C_{16}H_{34}S_2$. Found 290.2146.

*Dicyclohexyl disulfide (**2d**)*. IR (KBr) cm^{-1} 3000-2900 C-H (aliph., stretch), 1200-1100 C-S (stretch). ^1H NMR (300 MHz, $CDCl_3$) δ 2.5 (m, 2 H), 1.65 (dt, 8H), 1.4 (m, 12H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 52.56, 34.52, 26.59, 25.38. HRMS calcd 230.1235 for $C_{12}H_{22}S_2$. Found 230.1232.

*Disulfanyl-acetic acid (**2e**)*. IR (KBr) cm^{-1} 3500-3200 COOH (stretch), 3000-2900 C-H(aliph, stretch), 1200-1100 C-S (stretch). ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 4H), 11.5 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 35.81 (t), 179.91 (s). HRMS calcd 181.9714 for $C_4H_6S_2$. Found 181.9717.

*Diphenyl disulfide (**2f**)*. IR (KBr) cm^{-1} 3200-3100 C-H (Ar, stretch), 1200-1150 C-S (stretch). ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 4 H), 7.25 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 133.21, 131.48, 130.25, 129.53. HRMS calcd 182.0224 for $C_{12}H_{10}S_2$. Found 182.0226.

*Dinapth-2-yl disulfide (**2h**)*. IR (KBr) cm^{-1} 3200-3100 C-H (Ar, stretch), 1200-1150 C-S (stretch). ^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (s, 2 H), 7.7 (d, 2H), 7.5 (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. HRMS calcd 318.0512 for $C_{20}H_{14}S_2$. Found 318.0509.

RESULTS AND DISCUSSION

The oxidative coupling of thiols with the TPFAC reagent was investigated in dichloromethane at room temperature and under microwave irradiation using a minimal amount of solvent (acetonitrile). As shown in Table 1, a series of aliphatic and aromatic thiols could be reacted with 1 molar equivalent of the reagent to afford the corresponding disulfides in excellent yields. This oxidation could also be performed under microwave conditions with the TPAFC reagent. The results show that under microwave conditions, reaction times were shorter.

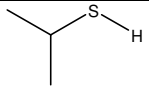
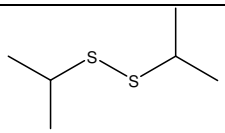
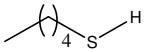
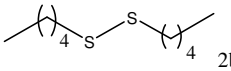
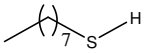
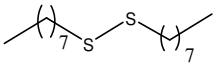
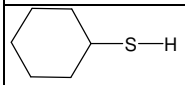
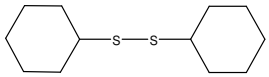
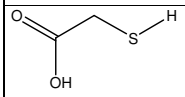
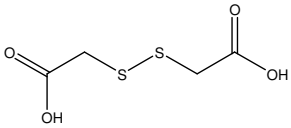
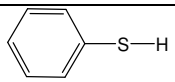
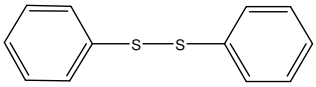
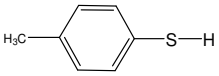
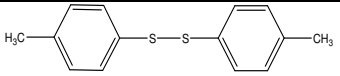
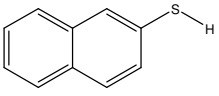
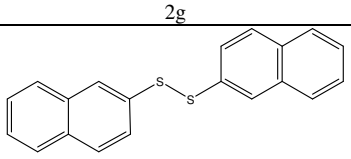
Microwave irradiation in these cases offers some advantages in terms of simplicity of performance, simple operation, no side product formation, very short reaction time and a wide range of substrates that could be converted to their corresponding disulfides.

TPAFC is a very versatile oxidant based on quaternary ammonium halochromates. In our research on oxidation processes, it has been found that TPAFC is an oxidant that is very well suited for microwave synthesis. As it is an ionic and magnetically retrievable material, it carries the benefit of an efficient conversion of electromagnetic energy into heat according to the dielectric heating mechanism (Table 1).

Mineral oxides are often very poor conductors of heat, but behave as very efficient microwave adsorbents, this resulting in turn in a very rapid and homogeneous heating. Consequently, they display very strong specific microwave effects, with significant

improvements in temperature homogeneity and heating rates, enabling faster reactions and less degradation of final products when compared to classical heating.

Table 1. Oxidation coupling of thiols (**1a**-**h**) with TPAFC in solution and under microwave irradiation using a minimal amount of solvent.

Substrate	In solution			Under microwave irradiation	
	Time (min)	Product	Yield (%)	Time (min)	Yield (%)
 1 a	55	 2a	75	6	85
 1b	54	 2b	78	7	85
 1 c	60	 2c	72	10	83
 1d	50	 2d	65	6	89
 1e	56	 2e	72	5	80
 1f	73	 2f	80	8	92
 1g	67	 2g	77	6	84
 1h	84	 2h	68	14	81

CONCLUSIONS

In conclusion, it has been found that TPAFC acts as a simple, efficient, and fast oxidizing reagent in the oxidative coupling of thiols. The easy procedure, simple work-up, the easy preparation of the reagent, short reaction times, and excellent yields of the products would make this reagent a useful addition to available oxidants. Also, it should be emphasized that the reactions can be performed cleanly and can be controlled to stop at the disulfide stage. Over-oxidation has not been observed, even when the reactions were carried out under different conditions. In this paper, we reported a procedure where the oxidation is performed in microwave irradiation, in order to prevent problems connected with conventional heating (cost, handling, safety, pollution, and decreases in reactivity by dilution of the reactants).

ACKNOWLEDGEMENTS

The authors are grateful to the Imam Khomeini International University research council for the support of this work and to Mr. K. Ghoddamy and Dr. K. Mahanpoor for their valuable comments.

REFERENCES

1. Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Wiley: New York; **1967-84**.
2. Jocelyn, D.C. *Biochemistry of the Thiol Group*, Academic Press: New York; **1992**.
3. Capozzi, G.; Modena, G.; Patai, S. *The Chemistry of the Thiol Group*, Wiley: New York; **1974**.
4. Lam, J.; Bildose, H.; Christensen, L.P.; Thomsen, T. *Acta Chem. Scand. Ser B*. **1989**, 43, 799.
5. Srivastav, V.; Gupta, R.; Guptam, R.R. *Ind. J. Chem.* B. **2000**, 39, 223.
6. Metzner, P. *Synthesis* **1978**, 669.
7. Holbrook, D.L. *Handbook of Petroleum Refining Processes*, Meyers, R.A. (Ed.), McGraw Hill: New York; **1996**; chap. 11.3.
8. Leitao, A.; Costa, C.; Rodrigues, A. *Chem. Eng. Sci.* **1987**, 42, 2291.
9. Papadopoulos, E.P.; Jarrar, A.; Issidoides, C.H. *J. Org. Chem.* **1966**, 31, 615.
10. Lopez, C.; Conzales, F.; Cossio, P.; Palomo, C. *Synth. Commun.* **1985**, 15, 1197.
11. Aizpurua, J.M.; Juaristu, M.; Lecea, B.; Palomo, C. *Tetrahedron* **1985**, 41, 2903.
12. Yoneda, F.; Suzuki, K.; Nitta, Y. *J. Org. Chem.* **1967**, 32, 727.
13. Nakagawa, K.; Shiba, S.; Horikawa, M.; Sato, K.; Nakamura, H.; Harada, N.; Harada, F. *Synth. Commun*. **1980**, 10, 305.
14. Firouzabadi, H.; Iranpoor, N.; Kiaeezadeh, F.; Toofan, J. *Tetrahedron* **1986**, 42, 719.
15. Ley, S.V.; Meerholz, A.; Barton, D.H.R. *Tetrahedron* **1982**, 38, 231.
16. Muathen, H.A. *Ind. J. Chem.* **1991**, 30B, 522.
17. McKillop, A.; Koyuncu, D.; Krief, A.; Dumont, W.; Renier, P.; Trabelsi, M. *Tetrahedron Lett.* **1990**, 31, 5007.
18. Tamamura, H.; Otaka, A.; Nakamura, J.; Okubo, K.; Koide, T.; Ikeda, K.; Fujii, N. *Tetrahedron Lett.* **1993**, 34, 4931.
19. Noureldin, N.A.; Coldwell, M.; Hendry, J.; Lee, D.G. *Synthesis* **1998**, 1587.
20. (a) Abramovitch, R.A. *Org. Prep. Proc. Int.* **1991**, 23, 683. (b) Majetich, G.; Hicks, R. *J. Microwave Power Electromagn. Energy* **1995**, 30, 27. (c) Caddick, S. *Tetrahedron* **1995**, 51, 10403. (d) Strauss, C.R.; Trainor, R.W. *Aust. J. Chem*. **1995**, 48, 1665.
22. (a) Bogdal, D.; Warzala, M. *Tetrahedron* **2000**, 56, 8769. (b) Bogdal, D. *J. Chem. Res. (S)* **1998**, 468. (c) Bogdal, D.; Pielichowski, J.; Jaskot, K.*Org. Prep. Proc*. **1998**, 30, 427.
23. Iranpoor, N.; Zeynizadeh, B. *Synthesis* **1999**, 49.