Tributylammonium Halochromates/silica Gel: Simple Reagents for Oxidative Coupling of Thiols to Symmetrical Disulfides

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New orange solid tributylammonium halochromates, $(C_4H_9)_3N^+CrO_3X^-$, TBAXC (X＝F, Cl) are easily synthesized by the reaction of tributylammonium fluoride and chloride with CrO_3 in a 1∶1 molar ratio in the presence of HF and HCl. Tributylammonium halochromates(VI) are versatile reagent for the effective and selective oxidation of organic substrates. Silica gel supported TBAFC and TBACC are versatile reagents for the effective and selective oxidation of organic substrates, in particular, thiols, under mild conditions. Considerable improvements are observed in the presence of the absorbent, making the work-up much more convenient.

Keywords tributylammonium halochromates, solid-phase synthesis, oxidation, silica gel, thiol, disulfide

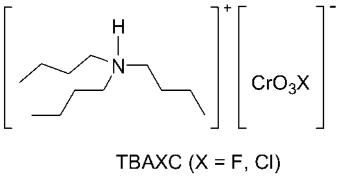
Introduction

Disulfides are one of the most important organic sulfur compounds possessing an exclusive chemistry both in biochemistry and in synthetic area.[1] 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 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.[2]

The main type of these reactions is the oxidation of thiols in the presence of manganese dioxide,[3] dichromates,[4] borohydride exchange resin,[5] DMSO/alumina reagent,[6] CBr_4/solid K_2CO_3/18-crown-6/benzene[7] and $NaIO_3$/alumina[8] and tetramethylammonium fluorochromate.[9]

However, some of the reported reagents suffer from disadvantages such as instability, hygroscopicity, low selectivity, long reaction time, difficulty of preparation and need for a large excess of the reagent. Thus a milder, more selective and inexpensive reagent is still in demand. Solutions to these problems lead to the development of a good number of other oxidants, such as pyridinium chlorochromate,[10] pyridinium fluorochromate,[11] quinolinium dichromate,[12] 2,2'-bipyridinium chlorochromate,[13] quinolinium chlorochromate[14] and isoquinolinium fluorochromate.[15] We synthesized tetramethylammonium fluorochromate[16] and cetyltrimethylammonium bromochromate (Scheme 1).[17] With the belief that, these reagents may have oxidative properties and could be used for oxidation of organic substrates.

Scheme 1



This manuscript introduces tributylammonium fluorochromate(VI) (TBAFC) and tributylammonium chlrochromate(VI) (TBACC) absorbed on silica gel, as new reagents with improved work-up efficiency and durability, for the oxidation of thiols to disulfides.

Experimental

Material and instruments

CrO_3 (Merck, p.a.) was used without further purification. Silica gel Aldrich, 150 mesh and merck Tlc plates were used. Solvents were purified by standard methods. Infrared spectra were recorded as KBr disks on a Shimadzu model 420 spectrophotometer. The UV/Vis measurements were made on an Uvicon model 922 spectrometer. ^1H and ^{13}C NMR were carried out on a Bruker AVANCE DRX 500 spectrometer at 500, 125 and 470.66 MHz, respectively using $SiMe_4$ as internal

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stamdarcl. 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 percent composition of carbon, hydrogen and nitrogen were obtained from the Microanalytical Laboratories of the Department of Chemistry, OIRC, Tehran.

Tributylammonium fluorochromate (TBAFC), $(C_4H_9)_3NH^+[CrO_3F]^-$

A sample of chromium(VI) oxide, CrO_3 (1 g, 0.01 mol) and of 40% hydrofluoric acid (0.9 mL, 0.02 mol) were added to 20 mL of water in a 100 mL polyethylene beaker with stirring. After 5 min, the homogeneous solution was cooled to *ca.* 0—2 ℃. To the resultant clear orange solution, tributylamine (0.235 mL, 0.01 mmol) was added drop wise with stirring over a period of 0.5 h and stirring was continued for 0.5 h at −4 ℃. The precipitated yellowish-orange solid was isolated by filtration on a polyethylene funnel, washed with petroleum ether (60 mL×3) and dried in vacuum for 2 h at room temperature. Yield 84%, m.p. 134 ℃, Anal. calcd for $C_{12}H_{28}CrFNO_3$: C 47.20, H 9.24, N 4.58; found C 46.92, H 9.64, N 5.20. IR (KBr): 914 [$\nu_1(A_1)$ or $\nu(CrO_3)$], 634 [$\nu_2(A_1)$ or ν(Cr-F)], 950 [$\nu_4(E)$ or $\nu(CrO_3)$] cm^{-1}. Electronic absorption at 22321 cm^{-1}, corresponding to ${}^1A_2 \rightarrow {}^1E$ (ε=177 L•mol^{-1}•cm^{-1}); 28735 m^{-1} to ${}^1E \rightarrow {}^1E$ (ε=701 L•mol^{-1}•cm^{-1}) and 35971 cm^{-1} to ${}^1A_1 \rightarrow {}^1E$ (ε=1314 L•mol^{-1}•cm^{-1}). UV/Visible, ^{13}C NMR and ^1H NMR, were all consistent with the TBAFC structure. The above procedure can be scaled up to larger quantities, if desired. The pH of 0.01 mol•L^{-1} solution of TBAFC in water was 3.15 (Scheme 1).

Tributylammonium chlrochromate (TBACC), $(C_4H_9)_3NH^+[CrO_3Cl]^-$

Chromium(VI) oxide (1.0 g, 0.01 mol) was dissolved in water in a beaker and 6 mol•L^{-1} hydrochloric acid (0.251 mL, 0.015 mol) was added under stirring at 0 ℃. To the resultant orange solution, tributylamine (0.235 mL, 0.01 mmol) was added dropwise under stirring over a period of 0.5 h and the stirring was continued for 0.5 h at −4 ℃. The precipitated orange solid was isolated by filtration, washed with petroleum ether 60 mL×3) and dried under vacuum for 2 h at room temperature. Yield 71%, m.p. 126 ℃. Anal. calcd for $C_{12}H_{28}ClCrNO_3$: C 44.79, H 8.70, N 4.35; found C 44.59, H 8.81, N 4.38. IR (KBr): 898 [$\nu_1(A_1)$ or $\nu(CrO_3)$], 436 [$\nu_2(A_1)$ or ν(Cr—Cl)], 940 [$\nu_4(E)$ or $\nu(CrO_3)$] cm^{-1}. UV/Visible and ^1H NMR were all consistent with the TBACC structure. Electronic absorption at 21881 cm^{-1}, corresponding to ${}^1A_2 \rightarrow {}^1E$ (ε=336 L•mol^{-1}•cm^{-1}); 28089 cm^{-1} to ${}^1E \rightarrow {}^1E$ (ε=891 L•mol^{-1}•cm^{-1}) and 34965 cm^{-1} to ${}^1A_2 \rightarrow {}^1A_1$ (ε=1178 L•mol^{-1}•cm^{-1}). The pH of 0.01 mol•L^{-1} solution of TBACC in water was 2.9.

General procedure for preparation of silica gel supported reagents

A 500 mL suction flask equipped with a constant-pressure dropping funnel was used. The cold solution of TBAFC or TBACC, prepared by complete solving of TEAXC (X=F, 0.2 mol, 44.2 g; X=Cl, 0.2 mol, 47.4 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 low pressure vacuum affords orange-red slurry, tributylammonium halochromates/silica gel, which is completely dried on the surface of highly dried day plate in the air.

Typical procedure for oxidation coupling of benzenethiol with tributylammonium halochromates/silica gel

A suspension of benzenethiol (**1f**) (0.110 g, 0.001 mol), TBAFC (0.221 g, 0.001 mol) and 0.2 g wet SiO_2 (50%, *w*) in CH_2Cl_2 (10 mL) was stirred magnetically at room temperature. The completion of the reaction was followed by TLC using ether/petroleum ether (V∶V=60∶40) as eluant. After its completion, the mixture was stirred in EtOH/$CHCl_3$ (V∶V=1∶3) solution for separating products from the solid support. This mixture allowed to stand for 1 h and then filtered, to give a clear solution. The solution was evaporated and the residual product purified by distillation, recrystallization or column chromatography to give 1,2-diphenyldisulfane (**2f**) in 79% yield in 123 min. m.p. 57—58 ℃ (Lit.[18] 58—60 ℃).

For other thiols (**1a**—**1e**, **1g**—**1h**), these procedures were the same as above. The same procedure was applied for coupling of benzenethiol to 1,2-diphenyldisulfane with TBACC and the above procedure could be achieved for large scales, without any problems.

1,2-Diisopropyldisulfane (2a)[18] ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.71 (d, J=7.0 Hz, 2H), 1.55 (d, J=8.0 Hz, 12H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 38.50 (d), 24.21 (q); IR (KBr) ν: 3000—2900 (C—H, aliph, strech), 1400—1350 (C—H, aliph bend), 1200—1100 (C—S, strech) cm^{-1}; HRMS calcd for $C_6H_{14}S_2$ (M^+) 150.4125, found 150.4117.

1,2-Dipentyldisulfane (2b)[18] ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.50 (t, J=7.4 Hz, 4H) ,1.62 (m, 4H), 1.25 (m, 4H) 1.33 (m, 4H), 0.85 (t, J=10.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 36.35, 33.13, 31.27, 23.53, 14.50; IR (KBr) ν: 2980—2900 (C—H, aliph, strech) 1200—1150 (C—S, strech) cm^{-1}; HRMS calcd for $C_{10}H_{22}S_2$ (M^+) 206.8542, found 206.1654.

1,2-Dioctyldisulfane (2c)[18] ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.61 (t, J=7.9 Hz, 4H) ,1.52 (m, 4H), 1.26 (m, 18H), 94 (t, J=7.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 33.66, 32.56, 31.43, 31.35, 31.22, 27.03, 23.51, 15.02; IR (KBr) ν: 2940—2900 (C—H, aliph, strech) 1150—1100 (C—S, strech) cm^{-1}; HRMS calcd for $C_{16}H_{34}S_2$ (M^+) 290.1213 found 290.3564.

1,2-Dicyclohexyl disulfane (2d)[18] ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.5 (m, 2H), 1.65 (dt, J=7.0 Hz, 8H), 1.43 (m, 12H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 52.56, 34.52, 26.59, 25.38; IR (KBr) ν: 2970—29020 (C—H, aliph, strech), 1200—1100 (C—S, strech) cm^{-1};

HRMS calcd for $C_{12}H_{22}S_2$ (M^+) 230.2135, found 230.2120.

Disulfanyl-acetic acid (2e)[18] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.27 (s, 4H), 11.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 35.28 (t), 179.19 (s); IR (KBr) ν: 3500—3200 (COOH, strech), 3050—2930 (C—H, aliph, strech), 1150—1100 (C—S, strech) cm^{-1}; HRMS calcd for $C_4H_6O_4S_2$ (M^+): 182.1478, found 182.3421.

1,2-Diphenyldisulfane (2f)[17] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.65 (d, J=10.0 Hz, 4H), 7.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 133.51, 131.44, 130.20, 129.53; IR (KBr) ν: 3200—3100 (C—H, Ar, strech), 1200—1150 (C—S, strech) cm^{-1}. Anal. calcd for $C_{12}H_{10}S_2$: C 66.13, H 4.71, S 29.37; found C 66.22, H 4.65, S 29.23.

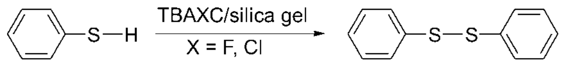
1,2-Di-*p*-tolyldisulfane or bis(4-methylphenyl)-disulfidev (2g) m.p. 42—44 ℃ (Lit.[19] 43—44 ℃); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.54 (d, J=10.5 Hz, 4H), 7.29 (d, J=12.0 Hz, 4H), 2.57 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 126.31 (s), 130.26 (d), 127.12 (d), 124.08 (s), 21.87 (q); IR (KBr) ν: 3200—3100 (C—H, Ar, strech), 2950—2900 (C—H, aliph, strech), 1480—1400 (C—H, Ar, bend), 1170—1050 (C—S, strech) cm^{-1}. Anal. calcd for $C_{14}H_{14}S_2$: C 68.29, H 5.70, S 26.14; found C 68.46, H 5.60, S 26.23.

1-(*n*-Naphthalene-3-yl)-2-(naphthalene-6-yl)disulfane (2h) m.p. 140—142 ℃ (Lit.[19] 142—145 ℃); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.11 (s, 2H), 7.74 (d, J=11.6 Hz, 2H), 7.53 (d, J=12.7 Hz, 6H) 7.32 (d, J=14.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 137.76, 137.11, 135.26, 134.52, 131.57, 128.92, 127.08, 126.16, 125.02, 124.87; IR (KBr) ν: 3140—3100 (C—H, Ar, strech), 1200—1150 (C—S, strech). Anal. calcd for $C_{20}H_{14}S_2$: C 75.47, H 4.40, S 20.12; found C 75.36, H 4.32, S 20.89.

Results and discussion

Different thiols were subjected to oxidations with tributylammonium fluorochromate(VI), (TBAFC) and tributylammonium chlrochromate(VI), (TBACC) absorbed on silica gel, in dichloromethane (Scheme 2).

Scheme 2



These oxidations take place under mild and completely heterogeneous conditions giving excellent yields (Table 1).

Oxidations may also occur using only TBAFC and TBACC, in the absence of silica gel, but considerable improvements were observed in the presence of solid support. These improvements are in the term of yields, removing hazardous organic solvents, simplified manipulation, easily separating the products and especially in the case of time of the reactions. This implies that the silica gel may act as a reaction medium, providing an effective heterogeneous surface area for the oxidation and at the same time, make the work up much more convenient. The strong electronic bind between the oxygen of SiO_2 in silica gel solid support and quaternary ammonium positive charge might occurred and probably could result in higher absorbent of reagents to solid support as compared to other similar reagents. The nature of the solvent does not appear to be particularly critical. Hydrocarbons, benzene, ethers and chlorinated hydrocarbons are equally effective with combination to ethanol to separate the product from the solid support. The practical choice is oriented by the solubility of the products and the desired reaction temperature. The chromium(VI) contents could be easily determined iodometrically. It is seemed from the Table 1 that TBAFC was more effective than TBACC for saturated organic thiols (**1a**—**1d**) especially in time of the reaction. This is probably due to higher electro negativity of fluore atom in TBAFC than TBACC.[16]

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.

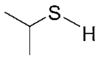
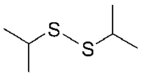
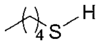
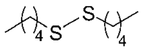
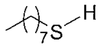
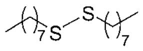
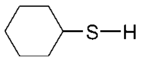
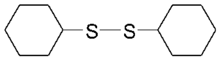
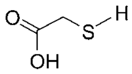
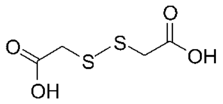
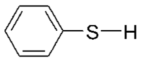
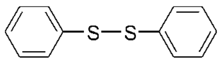
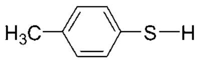
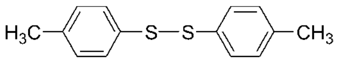
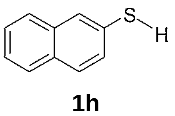
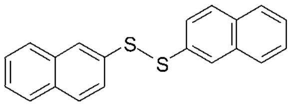
It is important to note that most of the previously reported methods for the oxidation of thiols use synthesized or toxic reagents and/or suffer from other disadvantages such as long reaction time and low yields,[3-9] but this method uses a readily available reagent and additionally offers the advantages of high yields, short reaction time, no side reactions, mild reaction conditions, a solid state reaction and simple isolation of the products. Consequently, this methodology should represent a good addition to list of methods already available for this purpose.

The IR spectra of TBAFC and TBACC are similar to that of other fluoro and chlorochromates.[19] TBAFC and TBACC are soluble in water, dimethylformamide, acetonitrile, acetone and dichloromethane, and only sparingly soluble in benzene, carbon tetrachloride, chloroform and hexane.

Conclusion

New reagents tributylammonium fluorochromate(VI) (TBAFC) and tributylammonium chlrochromate(VI) (TBACC) absorbed on silica gel are easily synthesized. They prove to be low cost, readily available oxidizing reagents for a variety of aromatic and none aromatic thiols. Their advantages include higher yields, shorter reaction time, lower thiol/oxidant molar ratios, and ease of separation of products. Moreover, during the reaction,

Table 1 Oxidation of thiols (**1a**—**1h**) with TBAFC and TBACC on silica gel

Entry	Substrate	Product	TBAFC		TBACC	
			Time/min	Yield/%	Time/min	Yield/%
1	 **1a**	 **2a**	115	78	150	91
2	 **1b**	 **2b**	65	74	77	68
3	 **1c**	 **2c**	68	90	80	91
4	 **1d**	 **2d**	84	82	152	89
5	 **1e**	 **2e**	60	88	212	85
6	 **1f**	 **2f**	42	79	38	92
7	 **1g**	 **2g**	28	93	34	89
8	 **1h**	 **2h**	41	81	50	92

the color of the oxidants change from orange to brown, thus providing a visual means for ascertaining the progress of the oxidation. This reaction is easily applicable for producing a minor to large amount of disulfides in simple and efficient procedure. Because of phase transfer properties of reagents, availability, versatility and high absorbance on silica gel by quaternary ammonium, these reagents, are suitable for oxidative coupling of thiols to disulfides. The mechanism of oxidation is probably similar to other quaternary ammonium reagents.[21] Many functional groups are inert towards these oxidizing agents, including, sulfides and phenols, enhancing the usefulness of the oxidants and the oxidation conditions for the synthesis of highly functionalized molecules.

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