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RESEARCH ARTICLE

Oxidation of thiols with methyltriphenylphosphonium dichromate (MTPPD) in dichloromethane at room temperature

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A chemoselective, straight-forward and rapid method for oxidation coupling of thiols to the corresponding disulfides using methyltriphenylphosphonium dichromate (MTPPD) in dichloromethane at room temperature. The reaction has been carried out in excellent yield and short reaction time.

Keywords: Thiols; Disulfides; Methyltriphenylphosphonium dichromate; Oxidation

1. Introduction

The oxidative coupling of thiols to the corresponding disulfides under mild conditions holds continued fascination from a biological and practical point of view [1]. Since thiols represent functional groups which can be over-oxidized, extensive research has been performed to control their oxidation [2].

The oxidation of thiols **2** to disulfides **3** is an important reaction in the synthesis of natural products, and further oxidation to disulfide S-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), and sulfonic acids is possible. Weak S−S bonds in these compounds impart high reactivity [3], and in natural products, these moieties and related cyclic analogues are associated with interesting biological activity [4]. Direct oxidation of disulfides has been reported using peroxides [5], periodate [6], dimethyl dioxirane [7], rhenium catalyst $[Re(O)Cl_3(PPh_3)_2]$ [8] and phenyl sulfoxide (Ph_2SO) [9]. Other methods for oxidation of thiols to the corresponding disulfide include using Fe(III)/montmorillonite/water/phosphate buffer [10], $Ca(OCl)_2$ [11], cetyltrimethylammonium dichromate [12].

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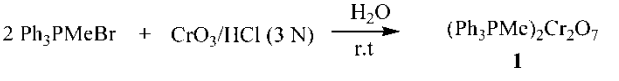
2. Results and discussion

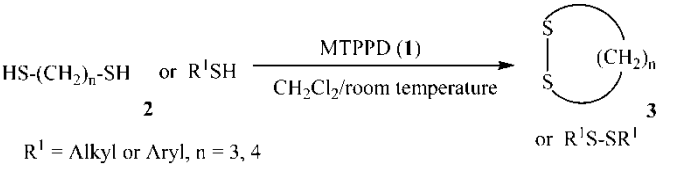
In connection to our ongoing program to introduce new reagents for oxidation of thiols under mild condition using benzyltriphenylphosphonium dichromate [13] and benzyltriphenylphosphonium peroxodisulfate [14], we wish to report the preparation of methyltriphenylphosphonium dichromate (MTPPD) **1** and he use of this efficient, inexpensive, stable and mild reagent for coupling a variety of aliphatic and aromatic thiols and aliphatic dithiols to their corresponding acyclic and cyclic disulfides. This reagent is readily prepared by the dropwise addition of CrO_3 in 3 M HCl to an aqueous solution of methyltriphenylphosphonium bromide at room temperature. Filtration and drying of the precipitate produced an orange powder in 96% yield, which could be stored for months without losing its oxidation ability. This reagent is quite soluble in methylene chloride, chloroform, acetone, THF, DMF, DMSO, and acetonitrile and insoluble in non-polar solvents, such as carbon tetrachloride, n-hexane, and diethyl ether (scheme 1).

Mixing equimolar amounts of **1** and thiol in solvent lead to the rapid formation of the corresponding disulfide. This method is a remarkably effective for oxidation of aliphatic and aromatic thiols to the corresponding disulfides. Reagent **1** also exhibits synthetic usefulness for producing cyclic disulfides from dithiols. The oxidation of dithiols results in the formation of cyclic and/or polymers disulfides. The polymers result from intermolecular oxidation, while the cyclic disulfides arise from intramolecular oxidative coupling of dithiols. For example, oxidative coupling of 1,4-benzenedimethanethiol gives only polymeric product (table 1), while 1,3-dithiol gives 75% cyclic disulfide and 25% polymeric products, the butane 1,4-dithiol gives only cyclic disulfide in 90% yield. It was found that the amount of further oxidation of producing disulfide to S-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), or sulfonic acid is minimal. A series of thiols were oxidized to disulfides rapidly by this reagent (table 1). Primary alcohol, amine, carboxylic acid, ester, and methoxy functional groups were unaffected during the oxidation of the thiols. The dithiols were oxidized to the corresponding cyclic disulfides in good yields (scheme 2 and table 1).

In conclusion, in this study we have introduced a new and mild reagent for oxidation of thiols or dithiol to the corresponding disulfides or cyclic disulfides. The stability, ease of preparation, straightforward work-up, mild reaction conditions, high yields of the products, and reaction at room temperature in short reaction time make this method a useful procedure for oxidation of thiols and dithiols to disulfides.

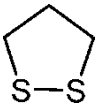
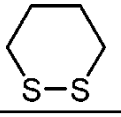


SCHEME 1



SCHEME 2

Table 1. Oxidation of thiols **2** with reagent **1** to disulfides **3** in dichloromethane at room temperature.[a,b,c]

Reactant (**2**)	Product (**3**)	Reaction time (min)	Yield (%)	Mp or bp/mmHg°C (Lit) [15]
C_6H_5SH	$(C_6H_5S)_2$	2	96	59–61 (59–61)
4-MeC_6H_4SH	(4-$MeC_6H_4S)_2$	3	90	47–48 (47–48)
4-$MeOC_6H_4SH$	(4-$MeOC_6H_4S)_2$	4	85	44–45 (44–45)
4-$NH_2C_6H_4SH$	(4-$NH_2C_6H_4S)_2$	3	80	76–77 (75–77)
3-MeC_6H_4SH	(3-$MeC_6H_4S)_2$	2	96	−21 (−21)
4-ClC_6H_4SH	(4-$ClC_6H_4S)_2$	5	94	72–73 (72–73)
2-$Me_2OCC_6H_4SH$	(2-$MeOOCC_6H_4S)_2$	2	98	197–198 (198–199)
$C_6H_5CH_2SH$	(C_6H_5 $CH_2S)_2$	4	95	69–70 (69–70)
4-$NO_2C_6H_4SH$	(4-$NO_2C_6H_4S)_2$	4	90	177–178 (172–178)
2-PyridylSH	(2-PyridylS)$_2$	3	95	52–53 (52–53)
4-PyridylSH	(4-PyridylS)$_2$	5	90	76–77 (76–77)
CyclopentylSH	(CyclopentylS)$_2$	3	94	105–106 (105–106)
CyclohexylSH	(CyclohexylS)$_2$	5	91	124 129 (124–129)
HO−CH_2CH_2SH	(HO−$CH_2CH_2S)_2$	5	93	Thick oil (156–1148/2)
$H_2OCCH_2CH_2SH$	($HOOCCH_2CH_2S)_2$	4	92	157–159 (157–159)
$HOOCCH_2SH$	($HOOCCH_2S)_2$	5	95	139–141 (138–139)
$CH_3(CH_2)_3SH$	($CH_3(CH_2)_3S)_2$	3	82	94–96/6 (94–96/6)
$CH_3(CH_2)_4SH$	($CH_3(CH_2)_4S)_2$	4	80	oil (117–119/6)
$CH_3(CH_2)_6SH$	($CH_3(CH_2)_6S)_2$	6	94	oil (152–154/6)
$CH_3(CH_2)_7SH$	($CH_3(CH_2)_7S)_2$	5	91	Semi solid (143–147/5)
1-$(HSCH_2)_2C_6H_4$	(−$SCH_2C_6H_4CH_2S−)_n$	6	92	–
$SH(CH_2)_3SH$		10	75	45–47/6 (45–47)
	(+ (−$SH(CH_2)_3S−)_n$)		(25)	65–70 (65–70)
$SH(CH_2)_4SH$		10	90	32–33 (32–33)

a) Confirmed by comparison with authentic samples (IR, TLC, and NMR); b) oxidant/thiol (1.0:1.0); c) yield of isolated pure product after chromatography or distillation.

3. Experimental

3.1 *General*

Yields refer to isolated pure products after column chromatography. The products were characterized by comparison of their spectral (IR, ^{1}H NMR) and physical data with those of authentic samples [15]. All ^{1}H NMR spectra were recorded at 300 MHz and 500 MHz in $CDCl_3$ relative to TMS (0.00 ppm) and IR spectra were recorded on Shimadzu 435 IR spectrometer. All reactions were carried out at room temperature in a hood with strong ventilation. The reaction is safe and we did not observe any dangers using this procedure under. Chromium can cause primary irritation, ulceration and allergic eczema when directly contacted with the skin and nasal and pulmonary irritation, with possible bronchogenic carcinoma upon breathing of chromate dust. Oral ingestion produces violent gastrointestinal irritation with vomiting and diarrhea.

3.2 *Preparation of MTPPD*

To a solution of methyltriphenylphosphonium bromide (100 mmol, 35.7 g) in water (50 ml) was added a solution of CrO_3 (100 mmol, 10.0 g) in HCl 3 N (50 ml) under stirring at room

temperature, after 15 min stirring, an orange precipitate was formed. The mixture was filtered, washed with water (2 × 15 ml), and dried at room temperature (38.5 g, 96% Yield), which decomposed at 220–222 °C to a dark-brown material. IR (KBr) 3100, 2980, 1600, 1495, 1480, 1260, 1190, 1050, 860, 750, 690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ, ppm: 7.9–7.7 (m, 15 H), 3.19 (d, $J = 14.6$, P−CH_3). ^{13}CNMR: δ 134.5, 134.4, 132.5, 132.3, 129.7, 129.3, 116.4. Anal Calcd for $C_{38}H_{36}Cr_2O_7P_2$: C: 63.16, H: 4.99%. Found C: 63.25, H: 4.90%.

3.3 *Procedure for oxidation of thiols to the corresponding disulfide compounds-. Typical procedure for oxidative coupling of thiols 2 to disulfides 3 with reagent 1*

In a round-bottomed flask (250 mL) equipped with a magnetic stirrer, a solution of thiophenol (10 mmol, 1.1 g) in CH_2Cl_2 (50 mL) was prepared. Reagent **1** (10 mmol, 3.7 g) was added to the solution and the resulting mixture was stirred magnetically at room temperature for 2 min. After completion of the reaction, monitored by TLC using EtOAc/cyclohexane (2:8), the reaction mixture was filtered and the solid material was washed with acetonitrile (50 × 2 mL). The solvent was removed under reduced pressure. The residue was purified by column chromatography using silica gel (EtOAc/cyclohexane, 2:8) to afford diphenyl disulfide in 96% yield, mp 59–61 °C [mp 58–61 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.62$–7.48 (m, 4H), 7.42–7.20 (m, 6H). IR (KBr): $\upsilon = 459, 470, 687, 734, 1435, 1474, 1572, 3050$ cm^{-1}.

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