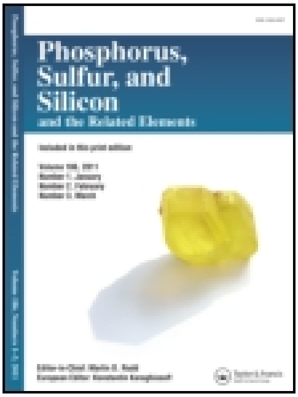

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Nasser Iranpoor [a] , Habib Firouzabadi [a] & Ali Reza Pourali [a]
[a] Department of Chemistry, Shiraz University, Shiraz, Iran

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Dinitrogen Tetroxide Impregnated Charcoal (N_2O_4/Charcoal): Selective Oxidation of Thiols to Disulfides or Thiosulfonates

Nasser Iranpoor
Habib Firouzabadi
Ali Reza Pourali
Department of Chemistry, Shiraz University, Shiraz, Iran

Selective oxidation of thiols to disulfides (RSSR) was performed by using catalytic amounts of dinitrogen tetroxide/charcoal in chloroform at r.t. while the reaction of thiols with four molar equivalents of the reagent in dichloromethane afforded thiosulfonates (RSO_2SR) with excellent yields.

Keywords Dinitrogen tetroxide; disulfides; oxidation; thiols; thiosulfonates

INTRODUCTION

Disulfides are of great importance in chemistry as well as in biochemistry.[1] Sulfur–sulfur bonds between cysteine residues stabilize three-dimensional structures of many peptides. Furthermore, organic compounds possessing disulfide and thiosulfonate functional groups are synthetically useful sulfenylating agents.[2]

The oxidation of thiols is the most exploited method for disulfide synthesis, mainly because a large number of thiols are commercially available and/or are easily synthesized. The selective oxidative coupling of thiols to disulfides is of interest from a synthetic perspective. Thiols are among functional groups, which can be easily over oxidized and, therefore, extensive methods have been reported for their controlled oxidation. Most of the existing methods involve the use of a stoichiometric amount of oxidants, such as oxo and peroxosalts,[3] halogens,[4] metal oxidants,[5] bis-tetra-*n*-buthylammonium thiosulfate,[6] dichlorodioxo molybdenum(VI)/dimethy sulfoxide,[7] diazenecarboxamides,[8]

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Address correspondence to Nasser Iranpoor, Shiraz University, Department of Chemistry, College of Sciences, Shiraz 71454, Iran. E-mail: iranpoor@chem.susc.ac.ir

clay-supported ferric nitrate,[9] silica sulfuric acid/sodium nitrite,[10] and peroxynitrite.[11] The catalytic oxidative coupling of thiols to disulfides in the presence of air or oxygen has great industrial importance in the purification of hydrocarbon raw materials to remove sulfur compounds, impairing the quality of motor fuels and poisoning catalysts in various stages of manufacturing synthetic rubber.[12] Some catalysts have been introduced for the oxidative coupling of thiols in the presence of oxygen or air, such as copper(I) dimercapto complexes,[12] iron(III)/sodium iodide,[13a] trifluroacetato titanium(IV) trichloride and *bis*-trifluroacetato titanium(IV) oxide/sodium iodide[13b] basic alumina,[14a] cesium fluoride/Celite,[14b] metal salts of 4-aminobenzoic acid/silica gel,[14c] copper nitrate dintrogen tetroxide[15a] hydrated copper nitrate,[15b] and tetrabutylammonium periodate/aluminum chloride.[16] Many of these methods suffer from long reaction times, undesirable side reactions, laborious isolation procedures, difficult preparation, or unavailability due to their reagents.

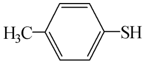
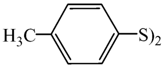
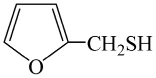
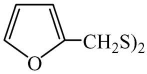
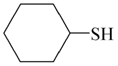
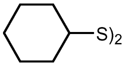
RESULTS AND DISCUSSION

Gaseous dinitrogen tetroxide has been reported to catalyze the formation of disulfides from thiols via *S*-nitrosothiols and an autocatalytic mechanism has been suggested for the decomposition of *S*-nitrosothiols in aerated solutions.[17]

Apart from difficulties in handling and the poisonous and corrosive nature of dinitrogen tetroxide, a further serious disadvantage of using dinitrogen tetroxide in organic synthesis is its high reactivity. In order to decrease its reactivity and avoid the formation of side products, low temperatures (that are strictly controlled) are always employed.[18]

In continuation of our program on the preparation and use of safe and solid supported forms of dinitrogen tetroxide in organic synthesis,[19] we recently reported dinitrogen tetroxide impregnated charcoal as a cheap, stable, and easily prepared reagent for the heterogeneous oxidation of sulfides, disulfides, benzylic alcohols, ethers, and nitrosation reactions.[20] By introducing dinitrogen tetroxide to a suspension of activated charcoal in dichloromethane, dinitrogen tetroxide/charcoal was obtained with a high capacity of dinitrogen tetroxide. In comparison to solid complexes of dinitrogen tetroxide that we have previously reported,[19a–e] this reagent has higher capacity. In addition to the cheapness and availability of charcoal for the preparation of this reagent, after completion of the reaction, no organic residue is produced from the reagent, which provides an easy work up. Dinitrogen tetroxide/charcoal is very stable in a refrigerator without loosing its activity for months.

TABLE I Catalytic Oxidative Coupling of Thiols (1.0 mmol) with Dinitrogen Tetroxide/Charcoal (0.2 mmol) in $CHCl_3$ at room temperature

Entry	Thiol	Product[a]	Time (min.)	Isolated yield %
1	$n\text{-}C_4H_9SH$	$(n\text{-}C_4H_9S)_2$	90	90
2	$sec\text{-}C_4H_9SH$	$(sec\text{-}C_4H_9S)_2$	120	80
3	$n\text{-}C_5H_{11}SH$	$(n\text{-}C_5H_{11}S)_2$	80	92
4	$n\text{-}C_8H_{17}SH$	$(n\text{-}C_8H_{17}S)_2$	100	85
5	C_6H_5SH	$(C_6H_5S)_2$	120	80
6	$C_6H_5\text{-}CH_2SH$	$(C_6H_5\text{-}CH_2S)_2$	140	90
7			60	96
8			80	82
9			220	80

[a]The products were characterized by their comparison with known compounds.[19f]

Now, we report the new applications of dinitrogen tetroxide/charcoal as a selective and efficient catalyst for the oxidative coupling of thiols to disulfides and/or as a selective reagent for the conversion of thiols to thiosulfonates. The catalytic coupling of thiols was performed with 0.2 molar equivalents of dinitrogen tetroxide/charcoal in the presence of oxygen in chloroform at room temperature (see Scheme 1, Table I).

$$\mathrm{RSH}\ \xrightarrow[\mathrm{O_2,\ r.t.,\ CHCl_3}]{\substack{\mathrm{N_2O_4/Charcoal}\\ \mathrm{(0.2\,mmol)}}}\ \mathrm{RSSR}$$

SCHEME 1

The use of this reagent provides the possibility of the catalytic oxidative coupling of thiols under mild and heterogeneous conditions. The produced disulfides are isolated with excellent purity and high yields.

Thiosulfonates (sulfonic *S*-esters) have shown valuable biological activities.[21a,b] Furthermore, thiosulfonates have a wide industrial application both in polymer production and in photographic processes.[21c,d] They have been reported to be strong sulfenylating agents, which react even faster than disulfides[22] and are extensively utilized in organic syntheses for sulfide and disulfide formation or aromatic thiocyanation with the thiolate anion.[2,23] However, the use of thiosulfonates has been limited by the lack of easy and practical preparations. Only a few routes are reported in the literature for their preparation from thiols.[18a,24] The synthesis of thiosulfonates from thiols with excess dinitrogen tetroxide at low temperatures (−20°C),[18a] [bis(trifluoroacetoxy)iodo] benzene,[24a] and sulfonyl chloride[24b] have been reported. The two first methods suffer from over oxidation of thiosulfonates into sulfonic acids as byproducts and good yields were obtained only when aromatic thiols were used. With the latter method, reaction of sulfonyl chlorides with heterocyclic aromatic thiols gives unsymmetrical thiosulfonates with moderate yields. Very recently we also reported on the use of tetrabutylammonium peroxymonosulfate/imidazole/manganese *meso*-tetraphenylporphyrin for this conversion.[24d]

The use of dinitrogen tetroxide/charcoal provides a suitable route for the direct preparation of thiosulfonates from thiols under mild and heterogeneous conditions with high yields. The workup of the reaction is very easy and thiosulfonates are isolated with excellent purity.

The one-pot conversion of thiols to thiosulfonates was achieved successfully in dichloromethane at r.t. using four molar equivalents of nitrogen tetroxide/charcoal (Scheme 2, Table II).

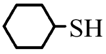
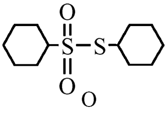
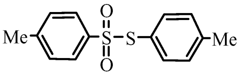
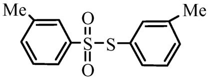
$$\mathrm{RSH}\ \xrightarrow[\mathrm{r.t.,\ CH_2Cl_2}]{\substack{\mathrm{N_2O_4/Charcoal}\\ \mathrm{(4\ mmol)}}}\ \mathrm{RSO_2SR}$$

SCHEME 2

The conversion of thiols to thiosulfonates occurs through the intermediacy of disulfide. This was demonstrated by analyzing the product mixture obtained from the reaction of thiophenol with an excess of dinitrogen tetroxide after 10 min. The analysis showed that a mixture of diphenyl disulfide and the corresponding thiosulfonate is obtained. In addition, the reaction of diphenyl disulfide with excess dinitrogen tetroxide produces the corresponding thiosulfonate.

In conclusion, dinitrogen tetroxide/activated charcoal as a safe, cheap, and easily available solid source of dinitrogen tetroxide acts as a stable oxidizing agent for sulfur compounds. The high efficiency and excellent selectivity of this reagent for the heterogeneous and selective oxidation of thiols to disulfides or thiosulfonates are considered as strong advantages of this method.

TABLE II Oxidation of Thiols to Thiosulfonates with Dinitrogen Tetroxide/Charcoal at room temperature

Entry	Thiol	Product[a]	Time (min.)	Isolated yield %
1	n-C_4H_9SH	n-$C_4H_9SO_2SC_4H_9$	30	95
2	n-$C_8H_{17}SH$	n-$C_8H_{17}SO_2SC_8H_{17}$	45	90
3	C_6H_5SH	$C_6H_5SO_2SC_6H_5$	60	98
4			60	88
5	4-$CH_3C_6H_5SH$		50	96
6	3-$CH_3C_6H_5SH$		65	95

[a] The products were characterized by their comparison with known compounds.[19f]

EXPERIMENTAL

General

Chemicals were purchased from Merck and Fluka Chemical Companies. The products were characterized by comparison of their spectral data with those of known samples. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates or by a Shimadzu Gas Chromatograph GC-14A instrument with a flame ionization detector.

Catalytic Oxidative Coupling of Thiophenol to Diphenyl Disulfide

To a stirred solution of thiophenol (0.11 g, 1 mmol) in pre-oxygenated $CHCl_3$(5 mL), catalytic amounts of N_2O_4/charcoal (0.05 g, 0.2 mmol) were added under an atmosphere of O_2 at r.t. The reaction mixture was stirred for 2 h and then was filtered. Evaporation of the solvent followed by purification of the product by chromatography on a short column of silica gel eluted with *n*-hexane, which afforded diphenyl disulfide (0.087 g, 80%), m.p. 61–63°C; (Lit.,[25] m.p. 61–62°C).

Oxidation of 4-Methyl Thiophenol to S-(4-Methylphenyl) 4-Methylbenzene Thiosulfonate

To the solution of 4-methyl thiophenol (0.124 g, 1 mmol) in CH_2Cl_2 (5 mL), the reagent (0.88 g, 4 mmol) was added with stirring at r.t. After 50 min., the reaction mixture was filtered. Evaporation of the solvent followed by chromatography on a short column of silica gel eluted with *n*-hexane/EtOAc (5:1), which gave *S*-(4-methylphenyl) 4-methylbenzenethiosulfonate (0.134 g, 96%); m.p. 74–75°C (Lit.[22] m.p. 73–75°C).

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