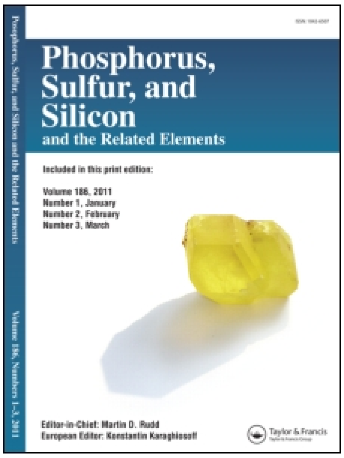

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Tungstate Sulfuric Acid: A Novel and Efficient Solid Acidic Reagent for the Oxidation of Thiols to Disulfides and the Oxidative Demasking of 1,3-Dithianes

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Tungstate sulfuric acid in combination with various oxidants was found to be an efficient reagent for the conversion of thiols to disulfides at r.t. in good to excellent yields. The selective oxidative deprotection of 1,3-dithianes to their parent carbonyl compounds at r.t. was also observed with this reagent.

Keywords 1,3-dithianes; disulfides; oxidation; thiols; tungstate sulfuric acid

INTRODUCTION

Currently, the heterogenation of chemical systems is an active field in industrial and laboratorial chemistry because of the simplification of handling procedures, reduction of corrosion, green chemistry point of view, avoidance of byproducts, easy and clean reaction, and simple work-up. With regard to the wide application of acids as reagents or catalysts in organic chemistry (for producing more than 1×10^8 mt/year of products), the introduction of new inorganic solid acids can be useful. Recently, silica sulfuric acid[1] and Nafion-H[2] have been used for a wide variety of reactions, such as the production of disulfides from thiols; the oxidation of 1,4-dihydropyridines;[3] the *N*-nitrosation of secondary amines;[4] the deprotection of acetals;[5] the oxidation of alcohols,[6]

Received; accepted.

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and the alkylation with olefins, alkyhalides, alkyl esters, isomerization, transalkylation, acylation, nitration, ether and ester synthesis, acetal formation, and rearrangement chemistry.[7]

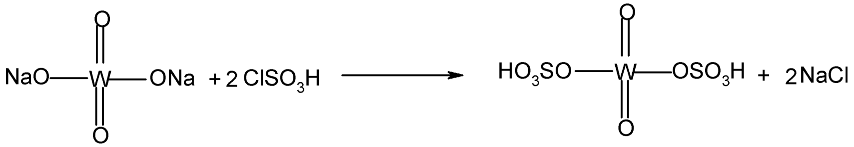
Disulfides play an important role in chemical syntheses. In biological systems, they control the cellular redox potential and prevent oxidative damage.[8–9] Several methods based on oxidative S-S coupling have been used for the synthesis of disulfides from thiols and protected thiols, including coupling with redox dyes, diazo compounds, sulfoxides, halogens, H_2O_2, $KMnO_4/CuSO_4$, $DMSO/I_2$, sodium perborate, $[Fe_4S_4(SR)_4]_2^-$, and electrochemical methods.[10]

1,3-dithiane and 1,3-dithiolane derivatives are versatile intermediates in the synthesis and interconversion of monocarbonyl and 1,2-dicarbonyl compounds. Thioacetals are often used as protecting groups for carbonyl compounds, particularly in multistep natural product syntheses, due to their stability toward both acidic and basic conditions. Many procedures are available in the literature for preparing thioacetals, but their deprotection to the parent carbonyl compounds is not always an easy process. In recent years, various hydrolytic[11] or oxidative methods have been reported for dethioacetalizations, and in the last two decades, numerous reagent combinations have been documented for the deprotection of thioacetals. Recently, we reported several methods for the deprotection of 1,3-dithianes under thermal and photochemical conditions.[12–14]

RESULTS AND DISCUSSION

In continuation of our studies[15] on the application of inorganic solid acids in organic synthesis, we have found that anhydrous sodium tungstate reacts with chlorosulfonic acid (1:2 mole ratio) to give Tungstate Sulfuric Acid (TSA) **1** as a new solid acid. The reaction is performed easy in a clean manner and without any work-up (Scheme 1).

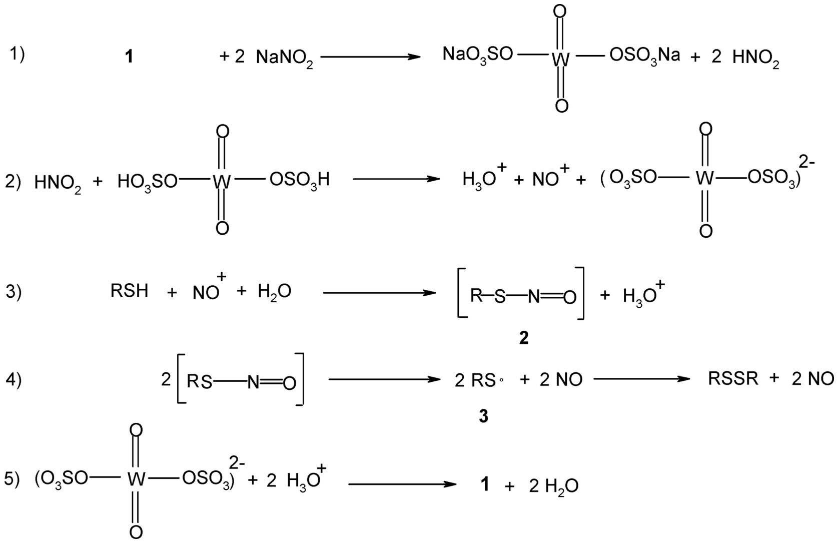
After the preparation of TSA **1**, we were interested to examine it as a proton source in combination with various oxidants in organic solvents. In this work we report a simple and practical method for



$$NaO-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{W}}-ONa + 2\,ClSO_3H \longrightarrow HO_3SO-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{W}}-OSO_3H + 2\,NaCl$$

1

SCHEME 1



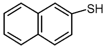
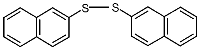
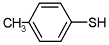
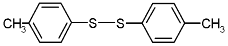
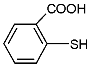
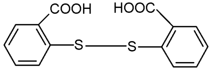
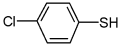
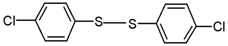
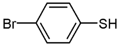
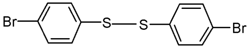
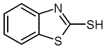
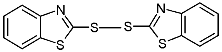
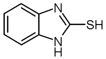
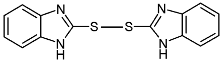
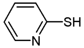
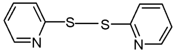
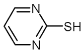
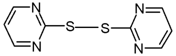
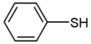
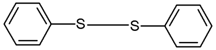
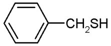
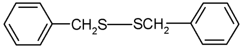
SCHEME 2

the effective oxidation of thiols to disulfides and for demasking 1,3-dithianes under mild and heterogeneous conditions. A variety of thiols were subjected to oxidation in the presence of wet **1** (10% w/w)/$NaNO_2$ in dichloromethane. Oxidation reactions were performed under mild and heterogeneous conditions. Immediately after the addition of the reactants in dichloromethane, a light-green color of the solution was observed, which disappeared quickly. We suggest that thionitrite **2** was formed, which converted to the related disulfides due to its instability under the reaction conditions. Based on other reports in the literature,[1,16–17] we propose that the reaction proceeds via the thiyl radicals **3** as reactive intermediates, with the formation of the disulfide by coupling these radicals (Scheme 2).

The proposed mechanism shows that TSA **1** acts as a catalyst. For increasing the rate of the reaction, we could use an excess of $NaNO_2$, but this was avoided because of probable nitrosation of the disulfides (Table I).

The ability of TSA **1** as a heterogeneous acidic reagent to catalyze the oxidative demasking of 1,3-dithianes in the presence of an oxidant was also investigated. The system consisting of wet **1** (10% w/w)/$KMnO_4$ in dichloromethane was investigated for the deprotection of a variety of 1,3-dithianes. The results showed that 1,3-dithianes undergo oxidative cleavage by sulfoxidation[18] and hydrolytic cleavage to yield the related carbonyl compounds (Table II, Scheme 3). It was interesting

TABLE I The Oxidation of Thiols to the Corresponding Disulfides With Wet 1/$NaNO_2$ in Dichloromethane at R.T.

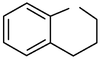
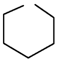
Thiol	Disulfide[a]	Time (min.)	Yield (%)[b]	M.P. (°C) Found (Lit.)
		10	98	144–146 (142–145)^{10a}
		7	96	43–44 (44–45)^{10a}
		50	90	286–287 (287–289)^{10b}
		20	95	72–73 (70–71)^{10a}
		7	98	90–92 (91–93)^{10a}
		5	90	177–179 (177–180)*
		5	90	200–201 (198–200)^{10b}
		5	90	55–56 (55–67)^{10a}
		5	90	133–135 (134–136)^{10c}
		15	95	59–60 (58–59)^{10a}
$CH_3(CH_2)_2CH_2SH$	$(CH_3(CH_2)_2CH_2S)_2$	18	94	Oil^{10b}
$CH_3(CH_2)_6CH_2SH$	$(CH_3(CH_2)_6CH_2S)_2$	20	93	Oil^{10b}
n-BuSH	$(n\text{-}BuS)_2$	20	92	Oil ^{10a}
c-$C_6H_{11}SH$	(c-$C_6H_{11}S)_2$	20	94	Oil^{10a}
		16	96	68–70 (70–71)^{10a}

[a] Identified by comparison with authentic samples.

[b] Refers to isolated yields.

*Chemical and Reagents 2005–2007 MERCK.

TABLE II The Oxidative Deprotection of 1,3-Dithianes With Wet 1/KmnO$_4$ in Refluxing Dichloromethane

R^1	R^2	Time (min.)	Yield (%)^a	M.P.(°C)^b Found (Lit.)
2-MeOC$_6$H$_4$	H	120	93	33–35 (34–37)
4-Br-C$_6$H$_4$	Me	70	95	49–50 (49–52)
4-Cl-C$_6$H$_4$	H	55	90	44–46 (46)
Ph	Ph	70	95	47–48 (47–49)
4-PhC$_6$H$_4$	Me	60	95	116–118 (118–121)
4-BrC$_6$H$_4$	CH$_2$Br	30	94	106–108 (107–110)
2-NO$_2$C$_6$H$_4$	H	120	91	42–43 (41–43)
3-NO$_2$C$_6$H$_4$	H	60	95	57–58 (58)
4-NO$_2$C$_6$H$_4$	H	60	92	105–106 (106)
4-Cl-C$_6$H$_4$	Ph	60	93	72–74 (73–75)
	—	60	90	oil
	—	40	80	oil
C$_6$H$_{13}$	H	30	81	oil

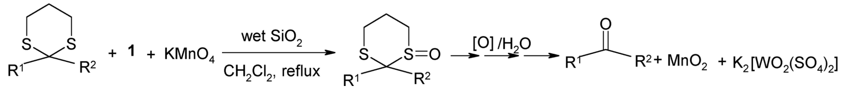
^{a}Refers to isolated yields.
^{b}Identified by comparison with authentic samples.[22]

that aldehydes were not further oxidized to the corresponding carboxylic acids (Table II). As shown in Table II, *ortho*-substituents make the oxidation of the dithianes slower, and therefore prolonged reaction times are needed. The presence of a bromine atom or of a methyl group ($R^2 = CH_3$, Br) leads to an increase of the rate of the final hydrolytic cleavage.

In conclusion, in this article we have reported the use of TSA **1** as a novel heterogeneous solid acid in a convenient, efficient, and practical method for the effective oxidation of thiols and oxidative deprotection of 1,3-dithianes. The availability of the reagents, easy and clean work-up, and high yields make this method a useful alternative to literature methodologies.

EXPERIMENTAL

Thiols and other chemicals were purchased from Merck, Fluka, and Aldrich. 1,3-dithianes were prepared from the corresponding carbonyl



SCHEME 3

compounds according to the reported procedure.[19] The reactions were monitored by TLC (silica-gel 60 F_{254},*n*-hexane:ethylacetate). Products were isolated and identified by comparison of their physical and spectral data with those of authentic samples.[1,10,16–17,20–22] IR spectra were recorded on a FTIR JASCO-680 spectrometer and ^{1}H NMR spectra were obtained with a Bruker DPX-300 instrument.

The Preparation of Tungstate Sulfuric Acid (1)

To 0.2 mol (23.3 g, 13.3 mL) of chlorosulfonic acid in a 250-mL round-bottom flask was cooled with an ice bath, and 0.1 mol (29.4 g) of anhydrous sodium tungstate was gradually added. After the completion of the addition, the mixture was shaken for 1 h, 10 mL cooled water was added, and the mixture was filtered under suction. A yellowish-white solid (TSA) 40.2 g (98.0%), m.p. 285 (dec.) was obtained. Characteristic IR bands (KBr, cm^{-1}); 3600–2200 (OH, bs), 1240–1140 (S=O, bs), 1060 (S-O, m), 1005 (S-O, m), 880–840 (W=O, m), 450 (W-O, m).

The Oxidation of Thiols: General Procedure

To a solution of 2 mmol of the thiol in 8 mL of dichloromethane, 0.5 mmol wet (10% w/w) TSA (**1**) and 1 mmol $NaNO_2$ were added. The reaction mixture was stirred at r.t. when a light-green heterogeneous solution was obtained rapidly, the color of which then disappeared. The progress of the reaction was monitored by TLC (n-hexane:ethylacetate). When the reaction was complete, the reaction mixture was filtered and washed with 4 mL of dichloromethane. The dichloromethane was removed by distillation using a water bath (40–50°C). The yields are summarized in Table I.

The Oxidative Deprotection of 1,3-Dithianes: General Procedure

To a solution of 1 mmol of the 1,3-dithiane in 4 mL of dichloromethane, 2 mmol $KMnO_4$ and 6 mmol wet (10% w/w) TSA (**1**) were added. The reaction mixture was stirred at r.t. when a brownish heterogeneous solution was obtained. The progress of the reaction was monitored by TLC (*n*-hexane:ethylacetate 8:2). When the rection was complete, the reaction mixture was filtered and washed with 4 mL of dichloromethane. The dichloromethane was removed by distillation using a water bath (40–50°C). The yields are summarized in Table II.

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