Sodium Tellurite as a Mild and Selective Oxidizing Agent for Thiols: Its Use in the One-Pot Synthesis of Unsymmetrical Disulfides

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Synopsis. Sodium tellurite acts as a mild and highly selective oxidizing agent for thiols under phase-transfer conditions at room temperature. Aromatic and benzylic thiols are rapidly converted to disulfides. Short-chain primary thiols undergo oxidation in preference to long-chain thiols. Secondary thiols are sluggish in oxidation and tertiary thiols remain intact. No overoxidation of the sulfur atom is observed. Similar results are also obtained with sodium tellurate.

Although thiols are easily oxidized to disulfides by a variety of reagents,[1,2] most of the conventional oxidizing agents lack the ability to differentiate thiols, i.e., aliphatic thiols from aromatic ones, or branched (*secondary* and *tertiary*) thiols from unbranched (*primary*) ones. Further oxidation often accompanies the reaction, leading to the formation of thiosulfinates and/or thiosulfonates. We now wish to report that sodium tellurite ($Na_2TeO_3 \cdot 5H_2O$)[3] exhibits a highly selective oxidizing ability for thiols under mild phase-transfer conditions. This reagent can convert instantaneously aromatic thiols and rapidly benzylic thiols to the corresponding disulfldes. Primary thiols are slow and secondary thiols are sluggish in oxidation, but tertiary thiols fail to react.

Recently, the reaction between Na_2TeO_3 and thiols has been reported to produce the tellurium(II) compounds of general formula $(RS)_2Te$ as a stable light yellow solid, difficultly soluble in alcohols and water.[4,5] However, as we describe herein, Na_2TeO_3 oxidizes thiols to disulfides under the liberation of free tellurium in the presence of a phase-transfer catalyst. Many sensitive functionalities were found to be inert toward Na_2TeO_3, which include amino, hydroxyl, azo, hydrazo, phenol, sulfide, disulfide, sulfoxide, aldehyde, olefinic and acetylenic bonds. Such inertness might be the main reason why Na_2TeO_3 has so far escaped from the attention of organic chemists as the reagent for organic transformations.

When an aqueous solution of Na_2TeO_3 was introduced dropwise into a stirred solution of benzenethiol (**1**) in benzene in the presence of a catalytic amount of tetrabutylammonium hydroxide at room temperature, the mixture quickly turned black due to the separation of free tellurium and gaschromatographic inspection revealed that the corresponding disulfide (**2**) was formed in high yield. No overoxidation of the sulfur atom was observed even in the presence of an excess of the reagent. The reaction was quite slow and incomplete in the absence of the phase-transfer catalyst.

$$\underset{\mathbf{1}}{C_6H_5SH} \xrightarrow[93\%]{Na_2TeO_3,\ Bu_4NOH/H_2O,C_6H_6,\ r.t.,\ 1\ h} \underset{\mathbf{2}}{H_5C_6SSC_6H_5}$$

Under similar conditions, primary and secondary alkanethiols are cleanly converted to disulfides in good to moderate yields (Table 1). However, ease of oxidation greatly depended on the nature of a carbon atom to which the thiol function is attached, the apparent general trend being $PhSH \approx PhCH_2SH > RCH_2SH > RR'CHSH \gg RR'R''CSH$. Short-chain thiols are apparently more reactive than long-chain ones. This may be partly attributable to the difference of solubility in water, and better results were obtained by using cetyltrimethylammonium bromide as a phase-transfer catalyst. Na_2TeO_3 oxidation of thiols may proceed through the initial formation of tellurium(IV) compounds of formura $(RS)_4Te$, followed by their stepwise decomposition to tellurium(II) and tellurium(0) species and the corresponding disulfides.[4,5]

Table 1. Na_2TeO_3 Oxidation of Thiols to *sym*-Disulfides

Thiol	Reaction time/h	Catalyst[a]	*sym*-Disulfide Yield/%[b]
C_6H_5SH	1	A	87 (93)
$2\text{-}H_2NC_6H_4SH$	4	A	88
$4\text{-}HOC_6H_4SH$	2	A	75
$C_6H_5CH_2SH$	1	A	88 (99)
$CH_3(CH_2)_2SH$	4	A	56 (94)
$CH_3(CH_2)_7SH$	48	A	77 (95)
$CH_3(CH_2)_7SH$	4	B	86 (90)
$(CH_3)_2CHSH$	48	A	48 (90)
$(CH_3)_3CSH$	24	B	0 (0)
$(CH_3)_3CCH_2(CH_3)_2CSH$	24	A	0 (0)

a) A and B refer to tetrabutylammonium hydroxide and cetyltrimethylammonium bromide, respectively. b) Yields refer to those of isolated compounds. Numerals in parentheses refer to GLC yields. Dodecane was used as an internal standard. All products are known and identified by spectral comparison with the authentic specimens.

Excellent ability of Na_2TeO_3 to differentiate types of thiols may well be exemplified by the efficient one-step synthesis of certain unsymmetrical disulfides. Thus, when a 9:10 mixture of phenylmethanethiol (**3**) and 2-methyl-2-propanethiol (**4**) was reacted with Na_2TeO_3 in the presence of tetrabutylammonium hydroxide for 36 h under the two-phase conditions, benzyl *t*-butyl disulfide (**5**) was obtained in 97% GLC yield. Isolated yield of pure product was 74%. Reaction between benzenethiol and 2-methyl-2-propanethiol gave the expected disulfide in an acceptable yield (Table 2). The former thiol rapidly disappeared, but the yield of the mixed disulfide did not improve even after prolonged reaction time. The unsymmetrical disulfides obtained showed no tendency to disproportionate and were unchanged after

Table 2. Oxidative Cross Coupling of Thiols to *unsym*-Disulfides

Thiol		Reaction time/h	Catalyst[a)]	*unsym*-Disulfide
RSH	R'SH			Yield/%[b,c)]
C_6H_5SH	$(CH_3)_3CSH$	24	A	52(74)
$C_6H_5CH_2SH$	$(CH_3)_3CSH$	36	A	74(97)
$CH_3(CH_2)_7SH$	$(CH_3)_3CSH$	24	B	81(89)
C_6H_5SH	$(CH_3)_2CHSH$	24	A	21(45)[d)]
$C_6H_5CH_2SH$	$(CH_3)_2CHSH$	24	A	56(78)

a,b) See footnotes in Table 1. c) Yields based on RSH. d) Diisopropyl disulfide formed in 14% GLC yield.

several months storage at room temperature.

$$\underset{\mathbf{3}}{C_6H_5CH_2SH} + \underset{\mathbf{4}}{(CH_3)_3CSH} \xrightarrow[97\%]{Na_2TeO_3,\ Bu_4NOH/H_2O,C_6H_6,\ r.t.,\ 36\ h} \underset{\mathbf{5}}{C_6H_5CH_2SSC(CH_3)_3}$$

The cross coupling between two different thiols no doubt proceeds through the initial conversion of the more reactive thiol to a symmetrical disulfide followed by the gradual thiolysis of the latter by the less reactive thiol.[6)] Since tertiary thiols are unreactive toward Na_2TeO_3, this method worked quite well for the synthesis of *t*-alkyl aryl disulfides and *n*-alkyl *t*-alkyl disulfides.[7)] The results were not very satisfactory for the synthesis of *s*-alkyl aryl disulfides (Table 2). Attempted cross coupling between primary alkanethiol and arenethiol led to a mixture of three possible disulfides in approximate ratio of 1 : 2 : 1, the unsymmetrical one predominating as expected.

Sodium tellurate ($Na_2TeO_4 \cdot 2H_2O$) exhibited a similar oxidizing ability for thiols. Since this compound is only slightly soluble in water, the reaction was carried out in a suspension in the presence of a phase-transfer catalyst. Under our conditions, no significant difference was observed between the oxidizing abilities of commercial Na_2TeO_3 and Na_2TeO_4. Both reagents are stable and easily handled solids, cheaply available as commercial products.

Experimental

All reagents were of commercial quality and purchased from Nacalai Tesque Inc. Reagent quality solvents were used without further purification. Column chromatography was carried out using Wakogel C-200. Gas liquid chromatography was run using a Shimadzu GC-14A apparatus with a CBP1-M25-025 capillary column (25 m).

Typical Procedure for the Oxidative Coupling of Thiols to Disulfides. Symmetrical Disulfide: To a stirred solution of phenylmethanethiol (0.629 g; 5.06 mmol) in benzene (20 ml) was added dropwise a solution of $Na_2TeO_3 \cdot 5H_2O$ (0.471 g; 1.51 mmol) and 10% aqueous tetrabutylammonium hydroxide (0.28 ml; 0.10 mmol) in water (20 ml) through a syringe at room temperature (25—30 °C). The reaction mixture quickly turned black and free tellurium began to precipitate. Monitoring by GLC indicated that the reaction was almost complete within 1 h. The mixture was filtered through a thin Celite bed and the organic layer was separated. The aqueous layer was extracted with benzene (20 ml×2) and the combined organic phase was washed with water (20 ml), dried over sodium sulfate, and evaporated. An oily residue was purified by chromatography on silica gel using hexane as the eluent to give dibenzyl disulfide (0.55 g; 88%); mp 71—72 °C (lit,[8)] 72 °C).

Unsymmetrical Disulfide: A solution of $Na_2TeO_3 \cdot 5H_2O$ (0.465 g; 1.49 mmol) and 10% aqueous tetrabutylammonium hydroxide (0.28 ml; 0.10 mmol) in water (20 ml) was added dropwise to a vigorously stirred solution of phenylmethanethiol (0.307 g; 2.47 mmol) and 2-methyl-2-propanethiol (0.251 g; 2.79 mmol) in benzene (20 ml). The resulting mixture was stirred for 36 h at room temperature and then worked up as described above to give pure benzyl *t*-butyl disulfide (0.39 g; 74% based on phenylmethanethiol) as an oil; bp 97 °C/0.9 mmHg (lit,[9)] 87 °C/0.3 mmHg).[#]

References

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[#] 1 mmHg=133.322 Pa.