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Simple Oxidation of Thiols with Sodium Iodate under Solid–Solution Biphasic Conditions†

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A variety of aromatic, aliphatic, and alicyclic thiols were readily oxidised with a combination of sodium iodate and chromatographic neutral alumina in hexane to afford the corresponding disulfides in excellent yields under mild and neutral conditions.

Much effort has been invested in realising selective oxidations of organic compounds.[1] The majority of conventional methods require the use of large amounts of heavy metal salts (Cr^{6+}, Pb^{4+}, Hg^{2+}, Tl^{3+}, Se^{4+} *etc.*) to effect the reactions, and therefore suffer frequently from the disposal problem of quantities of toxic wastes and a lack of economical applicability. When recent environmental and economical constraints[2] are taken into consideration, these processes may no longer be attractive as synthetic methods. Improved procedures are based either on the combined use of a metal salt as the catalyst and a *clean* reagent as the terminal oxidant or on the replacement of a stoichiometric oxidant with a *safer* reagent, thus reducing or eliminating toxic chemicals at source. In the latter context, it may be of considerable interest to use inorganic oxohalogen acid derivatives, since the reagents are inexpensive and safe to handle,‡ and the oxidant residues are in general environmentally compatible and can easily be removed from the final reaction mixtures.

Contrary to extensive investigation into periodate-based reactions,[4] sodium iodate ($NaIO_3$, **1**) appears to be less attractive as a laboratory oxidizing agent. Earlier reactions using **1**, of which we are aware, are those on the oxidative alkoxylation of 1,2-naphthoquinone,[5a] oxidation of dihydroxyarenes to quinones[5b] and of a number of functional groups[5c] under aqueous conditions. Consequently, those methods are unavoidably accompanied by laborious work-ups of products and production of large volume aqueous effluents. The latest work[5c] indeed included the oxidation of thiols at elevated temperature, but examined only two substrates, *viz*. **2e** and **2k** (see Scheme 1), and thus lacked generality; moreover, the yields of the disulfides were not indicated. Our previous observation that **1** in absolute methanol gives a facile oxidation of catechol to 4,5-dimethoxy-*o*-benzoquinone[6] might suggest that **1** can favorably be used in a dry medium. Consequently, we have tested the synthetic potential of **1** for the oxidation of thiols[7] in an aprotic solvent, since the new procedure could eliminate experimental problems inherent to this type of reagent.

An attempted reaction carried out by simply stirring a mixture of **1** and a thiol **2** in hexane, however, was sluggish and failed to give the disulfide **3** in a synthetically useful yield within a reasonable period of time. GLC analysis of the reaction mixture of benzenethiol **2a**, for example, showed that only 34% of diphenyl disulfide **3a** was obtained from a 1 h reaction at 20 °C and 66% of **2a** remained unreacted. Prolonged reaction achieved 100% conversion (*ca.* 3 h; **2a** 100%), but test runs at elevated temperatures (40 °C and under gentle reflux) resulted in decreased conversions (44 and 27%, respectively), and therefore $NaIO_3$ in hexane is unattractive for the present purpose. It might be expected that the oxidation could conveniently be performed under mild conditions within a shorter reaction period by making use of the catalytic effect of solid supports.[8] Thus, **2a** was then treated with **1** in the presence of untreated (commercial) and predried alumina for 30 min at 20 °C, but these reactions achieved only 20 and 18% conversions, respectively. On the other hand, use of alumina preloaded with an optimum amount of water (moist alumina) achieved 100% conversion. Filtration, followed by removal of the solvent gave a quantitative yield of **3a** with satisfactory purity (entry 1 in Table 1). Another control experiment performed under hexane–water biphasic conditions without adding alumina gave **3a** in only 55% yield, clearly indicating that moist alumina catalyses the reaction. It should be noted that the set-up of the moist alumina-based reaction and the work-up of the product are straightforward, and the reaction can be accomplished under much milder conditions than those of the earlier procedure.[5c] In addition, from environmental and economical points of view, use of hexane as the solvent should be favorable.

$$\underset{\mathbf{2}}{2\ R{-}SH} \xrightarrow[20\ ^{\circ}C,\ 0.5{-}2\ h]{NaIO_3,\ Moist\ alumina,\ Hexane} \underset{\mathbf{3}}{R{-}S{-}S{-}R}$$

2,3	R	**2,3**	R	**2,3**	R
a	Ph	**g**	2-ClC_6H_4	**m**	C_8H_{17}
b	4-$MeOC_6H_4$	**h**	3-ClC_6H_4	**n**	$C_{10}H_{21}$
c	2-MeC_6H_4	**i**	4-ClC_6H_4	**o**	$C_{12}H_{25}$
d	3-MeC_6H_4	**j**	4-$O_2NC_6H_4$	**p**	$C_{14}H_{29}$
e	4-MeC_6H_4	**k**	$PhCH_2$	**q**	*c*-C_5H_9
f	4-BrC_6H_4	**l**	C_6H_{13}	**r**	*c*-C_6H_{11}

Scheme 1

The $NaIO_3$/moist alumina system can successfully be used for the oxidation of substituted benzenethiols **2b**–**j**, regardless of the electronic properties of the substituents (entries 2, 5, 6, 9, and 10) and their positions on the benzene ring (entries 3–5 and 7–9). Aralkyl thiol **2k**, aliphatic thiols bearing medium to long alkyl chains **2l**–**p**, and alicyclic thiols **2q,r** also underwent smooth oxidation, affording the corresponding disulfides in nearly quantitative yields from 1–2 h reactions.

Oxidative coupling of **2** to **3** has been a subject of extensive research[7] and many reagent systems are currently available, but some limitations and/or difficulties in their performance have been pointed out.[9] The simple,

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‡Some safety assessments of sodium iodate have recently been made.[3]

Table 1 Oxidative coupling of thiols **2** to disulfides **3** with $NaIO_3$ and alumina[a]

Entry No.	t/h	Disulfide (%)[b]	Entry No.	t/h	Disulfide (%)[b]
1	0.5	**3a** (quant.)	10	0.5	**3j** (98)
2	0.5	**3b** (98)	11	1	**3k** (quant.)
3	0.5	**3c** (99)	12	1	**3l** (96)
4	0.5	**3d** (94)	13	1	**3m** (99)
5	0.5	**3e** (95)	14	1.5	**3n** (quant.)
6	0.5	**3f** (95)	15	1.5	**3o** (quant.)
7	0.5	**3g** (99)	16	1.5	**3p** (quant.)
8	0.5	**3h** (92)	17	1.5	**3q** (97)
9	0.5	**3i** (99)	18	2	**3r** (98)

[a] Under argon, at 20 °C; 1 mmol of thiol **2**, 2 mmol of $NaIO_3$, 1 g of freshly prepared moist alumina, and 10 ml of hexane were used in every run. [b] Isolated yield of disulfide **3** based on the starting material **2**.

inexpensive procedure demonstrated here gives a rapid, mild, clean oxidation of a wide range of thiols, and therefore could be a method of choice for the synthesis of symmetrical disulfides.

Experimental

General.—^{1}H NMR spectra were recorded with a JEOL PMX-60 (60 MHz) spectrometer for solutions in $CDCl_3$ using Me_4Si as an internal standard. Analytical GLC was performed on a Shimadzu GC-4CM instrument, equipped with a FID *via* a 2 m × 5 mm diameter glass column packed with 3% Silicone OV-17 on Uniport HP and interfaced with a Shimadzu Chromatopac C-R6A integrator, with temperature programming. Melting points were determined on a Yanagimoto MP-S3 melting point apparatus and are uncorrected. thiols **2a**–**r** and reagent grade $NaIO_3$ powder (Kanto Chemical, Japan) were used as received from commercial sources. Moist alumina (H_2O content, 17 wt%) was prepared by adding deionised water (0.2 g) in portions to oven-dried (500 °C, 1 h) chromatographic neutral alumina (ICN Biomedical, Alumina N, Super I; 1 g), followed by vigorous shaking of the mixture after every addition for a few min until a free-flowing powder was obtained.

Oxidation Procedure.—A 30 ml two-necked round-bottomed flask, equipped with a Teflon-coated stirrer bar, a reflux condenser, and a gas-inlet tubing connected to a dry argon-filled balloon, was arranged in order to conduct the reaction under a dry and inert atmosphere by linking the top of the condenser to a liquid paraffin trap *via* flexible silicone-rubber tubing. A general procedure is described for the oxidation of benzenethiol **2a**. Thus, the flask was charged with **2a** (0.100 g, 1 mmol), $NaIO_3$ (0.4 g, 2 mmol), freshly prepared moist alumina (1 g), and hexane (10 ml). After flushing the flask with argon, the resultant heterogeneous mixture was maintained at 20 °C while efficient stirring was continued in order to ensure a smooth reaction and to attain reproducible results. After 30 min, the whole material was transferred onto a sintered glass funnel and the filter cake was washed thoroughly with portions of dry diethyl ether (total 50 ml). Rotary evaporation of the solvent left pure (^{1}H NMR, GC, and TLC) diphenyl disulfide **3a** in quantitative yield (0.109 g, mp 57–58 °C; reported mp[10] 58–60 °C).

Oxidations of the other thiols **2b**–**r** were carried out as above, reaction periods of which were determined on the basis of reactivity of the thiols and yield of disulfides **3b**–**r**. In cases where coloured (pale to deep yellow depending on substrates) products were obtained, a single chromatography on a silica gel column (Merck silica gel 60, hexane) discharged the colour and gave disulfides with satisfactory purities (>98%).

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