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Facile Solvent-free Oxidation of Thiols Mediated by Mineral Supports

Laurent Sainte-Marie [#], Eryka Guibé-Jampel [*] and Michel Therisod [#]

[*] Lab. Réactions Sélectives sur Support and [#] Lab. Chimie Bioorganique et Bioinorganique,
I.C.M.O. - Bat. 410-420, Université Paris-Sud, F-91405 Orsay cedex.

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Abstract: Oxidation of thiols dispersed without solvent on a weakly basic mineral support was easily performed by heating in air.

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Oxidation of SH to S-S groups is well documented. Various oxidants have been employed for this conversion: H_2O_2, hydroperoxides, peracids, halogens, polyvinylpyridine-bromine, metal ions or metal oxides, molecular oxygen in the presence of strong bases [1]. Recently, an enzyme-mediated oxidation was reported [2]. All these procedures occur in water or in organic solvents. However, oxidation of aromatic thiols bearing electron-withdrawing groups requires long reaction times and strongly basic conditions. Consequently, there is a need for protocols using readily available, safe and cheap reagents, leading to general and selective oxidation of thiols in good yields. We considered that oxidation in dry conditions mediated by mineral supports (silica, Celite, Florisil, alumina, Hyflo Super Cel® (HSC), could be an interesting alternative.

We wish to report the preparation of disulfides by heating the coresponding thiols dispersed or impregnated on HSC or Florisil.(a weakly basic support with pH 8.5 - 9), in the presence of air (Table 1).

$$2\ \underset{\mathbf{1}}{\text{R-SH}} \xrightarrow[(\Delta \text{ or } \mu\text{w}),\ 5\text{-}30 \text{ min.}]{\text{Air, mineral support}} \underset{\mathbf{2}}{\text{R-S-S-R}}$$

Since we had found in our previous studies that focused microwave irradiation is the best method for homogeneously heating solid mixtures with continuous control of power or temperature [3], we performed the first experiments using a microwave reactor. Under controlled power, the temperature reached a plateau after a few minutes, then went down when the less polar disulfide was formed. For instance, for the oxidation of mercaptopyridine (entry 5) under 300 W, the temperature reached 155° after 9 min, remained constant for 3 min, then went down. The conversion was complete after a total reaction time of 12 min. We considered the maximum temperature reached in these experiments as optimal conditions for the classical heating. Indeed, both methods gave good purities and quantitative yields. However, in the case of high melting thiols, the temperature reached by MW irradiation was not sufficient for complete oxidation, and classical heating was a better choice (thiosalicylic acid, entry.12, 14). Reaction rates and yields strongly depend on the degree of loading of the support. Good yields were obtained with a thiol/support ratio up to 1/3 w/w. At higher ratios, the rate of diffusion probably becomes the limiting factor. With a thiol/support ratio lower than 1/4, the reaction was always completed in less than 30 min. Other supports like silica-gel or Celite could be used, but the reaction proceeds slower. Virtually no reaction occurs without support, when the molten thiol is simply heated in an oil bath or by μw irradiation (entry 10, 13, 15). Poor yields are obtained by heating a long time at a lower temperature. No reaction occurs when the supported thiol is heated under a stream of argon, which indicates that the oxidant is air (entry 15). The process is not successful with thiols such as 2-mercaptothiazoline and thiouracil, probably because the tautomeric equilibrium for a thiol form does not take place without solvent).

Email: therisod@icmo.u-psud.fr; eriguibe@icmo.u-psud.fr

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Table 1. Oxidation of thiols **1** into disulfides **2**

Entry	Thiol 1	T°,	time[a] (min)	Thiol/support w/w (%)	Yield of 2	Mode[c]
1	p-Nitrothiophenol	140	15	25	>98	μw
2	""	165	15	50	75	""
4	""	150		25	>98	""
5	2-Mercaptopyridine	155	12'	16	>98	""
6	""	175	15	25	90	""
7	""	210	15	50	57	""
8	""	215	15	60	50	""
9	""	200	30	60	85	""
10	""	255	6	100[b]	0	""
11	""	165	15	25	>98	Δ
12	Thiosalicylic acid	95	30	16	33	μw
13	""	90	30	100[b]	<10	""
14	""	180	20	25	>98	Δ
15[d]	""	180	30	25	<3	""
16	"".	180	60	100[b]	<10	""
17	p-Chlorothiophenol	100	30	25	>98	""
18	2-Mercapto-benzothiazole	190	30	25	>98	""
19	2-Mercaptothiazoline	130	30	25	0	""
20	2-Thiouracil	190	30	25	0	""

a: Maximum temperature reached under μw irradiation, or imposed temperature under classical heating; b: No support; c: Microwave-irradiation (μw) or classical heating (Δ); d: Under argon.

In conclusion, thiols can be quantitatively oxidized into disulfides in a very short time by simple heating on a weakly basic mineral support in the presence of air.

Experimental: Reaction mixtures were prepared by mechanical dispersion of the thiol on the support (Hyflo Super Cel®, Fluka) with a vortex mixer, or by impregnation of the support with a thiol solution in either, methylene dichloride or methanol. Oxidation was performed in an open vessel, in a microwave reactor Synthewave 402 (Prolabo) or in a preheated oil bath. After the reaction, the coated support was eluted with an appropriate solvent. After drying, the support could be reused without loss of activity. The products were identified by NMR, MS and by comparison with authentic samples. There was no evidence of the presence of side-products.

References:

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