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An Efficient and Selective Solid State Oxidation of Thiols to Disulfides with Quinolinium Fluorochromate on Silica Gel

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Summary. Various kinds of aliphatic (cyclic and acyclic), aromatic, and heterocyclic thiols are converted into the corresponding disulfides by quinolinium fluorochromate (*QFC*) on silica-gel in excellent yields. Selective oxidation of thiols in the presence of sulfides is also achieved under solid phase conditions.

Keywords. Quinolinium fluorochromate; Thiols; Oxidations; Chemoselectivity; Solid state.

Introduction

Transformation of thiols to disulfides is important from both synthetic and biochemical points of view, and accordingly, numerous studies have been reported [1–15]. This conversion has been accomplished using a variety of reagents such as molecular oxygen [2], metal ions [3], metal oxides [3a], *DMSO* [4], nitric oxide [5], halogens [6], sodium perborate [7], electrochemical oxidation [8], clayfen [9], borohydride exchange resin transition metal salt systems [10], morpholine iodine complex [11], pyridinium chlorochromate [12], aqueous HIO_3 [13], ammonium persulfate [14], *Caro*'s acid supported on silica-gel [15], and horseradish peroxidase or mushroom tyrosinase [16]. Most of the reagents involve solvents in protocols that lack the general applicability to thiol substrates bearing alkyl, aryl, and heterocyclic moieties. There is increasing emphasis on technological developments for reactions proceeding in the absence of solvent [17] or utilizing mechanochemical techniques [18]. Recently, we have reported several chromium(VI) based

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$$R\mathrm{SH} \xrightarrow{\text{A or B}} R\mathrm{SS}R$$

A: *QFC*/SiO_2, rt
B: *QFC*, CH_3CN, rt

Scheme 1

oxidants for oxidative transformations under nonaqueous and or solvent-free conditions [19]. In connection with our ongoing work on new applications of chromium(VI) based oxidants we herein report a facile oxidation of thiols to disulfides in solution and under solvent-free conditions using *QFC* (Scheme 1).

Results and Discussion

QFC is easily prepared from quinoline, 40% hydrofluoric acid, and chromium(VI) oxide in a molar ratio of 1:1.5:1 [20]. This reagent is red-orange, crystalline, non-hygroscopic, and air-stable. It can be stored in a sealed polyethylene bag for long periods without decomposition. Oxidative coupling of different types of aliphatic (cyclic and acyclic), aromatic, and heterocyclic thiols was investigated in the absence of solvent with *QFC* (Table 1). In an easy procedure *QFC* supported on silica-gel and thiols were mixed together in a mortar and left for an appropriate period without any further agitation. All of the thiols reacted efficiently and the corresponding disulfides were isolated in excellent yields. No over-oxidation was observed, even when the reactions were carried out with an excess of the reagent and in different solvents. In order to compare the results with those of experiments in solution, we studied the reactions in acetonitrile. As shown in Table 1, there are appreciable differences in the reaction time between the results obtained in solution

Table 1. Oxidation of thiols to disulfides using *QFC*[a]

Entry	Thiol	Oxidation in acetonitril		Solvent free condition	
		Time/h	Yield[b]/%	Time/min	Yield[b]/%
1	Benzenethiol	1.5	96	20	95
2	4-Methylbenzenethiol	1.4	91	15	93
3	4-Chlorobenzenethiol	1.5	94	25	90
4	Benzylhydrosulfide	1.8	90	30	92
5	Cyclohexanethiol	1.2	94	20	94
6	2-Sulfanylacetic acid	1.2	89	20	92
7	2-Pyridinethiol	0.5	97	–[c]	96
8	Butanethiol	1.6	92	25	94
9	Octanethiol	1.8	91	30	88
10	1*H*-Benzimidazole-2-thiol	2.5	85[d]	60	87
11	Benzthiarole-2-thiol	1.9	90	25	90

[a] All of the products were characterized by comparison of their spectral and physical data with those of authentic samples; [b] isolated yields; [c] reaction occurs immediately; [d] mole ratio *QFC*/thiol = 2:1

Table 2. Oxidative coupling of thiols by *QFC*/SiO_2 in comparison with other reagents

Substrate	Reagent (solvent)	Ratio of reagent/ substrate	Time/min	Yield/%	Ref.
Cyclohexanethiol	*QFC*/SiO_2 (Solid phase)	1:1	20	94	–
2-pyridinethiol	*QFC*/SiO_2 (Solid phase)	1:1	–[a]	96	–
Cyclohexanethiol	*PCC*[b] (Dichloromethane)	1:1	180	86	[12]
Cyclohexanethiol	*BER*[c] + $CuSO_4$ (Methanol)	0.5:1	180	99	[10]
2-pyridinethiol	*BER*[c] + $CuSO_4$ (Methanol)	0.5:1	540(360)[d]	94(98)[d]	[10]
Cyclohexanethiol	$(NH_4)_2S_2O_8$ (Solid phase)	1.1:1	20	89	[14]
2-pyridinethiol	$(NH_4)_2S_2O_8$ (Solid phase)	1.1:1	10	83	[14]
Cyclohexanethiol	Sodium perborate (Aqueous methanol)	2:1	120	92	[7]
2-pyridinethiol	Sodium perborate (Aqueous acetic acid)	2:1	120	75	[7]
Cyclohexanethiol	*Caro*'s acid/SiO_2 (Acetonitrile)	1:1	510	96(100)[e]	[15]

[a] Reaction occurs immediately; [b] pyridinium chlorochromate; [c] borohydride exchange resin; [d] under a stream of nitrogen; [e] yield based on GC analyses

and under solvent-free conditions. An advantage of the reagent is the exclusive oxidation of thiols irrespective of the presence of sulfides. When a mixture of equimolar amounts of thiophenol and thioanisole was treated with *QFC*, only the thiol was selectively oxidized to the corresponding disulfide and the sulfide remained unchanged.

The advantage of using *QFC* on silica-gel as a solid state method of coupling thiols to the corresponding disulfides is illustrated in Table 2. Thus, the oxidation of thiols with *QFC* on silica-gel is superior to other methods in terms of molar ratio, yields, easier isolation of the products, and shorter reaction times.

In conclusion omitting the solvent in oxidative coupling of thiols by *QFC* on silica-gel reduces the reaction time, the need of using the solvent is suppressed, and the workup procedure becomes easier. This work demonstrates a new, useful, and selective method for the oxidation of thiols to disulfides.

Experimental

All products were identified by comparison of their physical and spectral data with those of authentic samples. IR spectra were determined on a SP-1100, P-UV-Com instrument. ^1H NMR spectra were recorded with a EM 360 A (60 MHz) spectrometer. *QFC* was prepared as described previously [19].

General Procedure for Oxidative Coupling of Thiols by Quinolinium Fluorochromate on Silica Gel

QFC (0.249 g, 1 mmol) was mixed with 1 g of SiO_2, 1 mmol of thiol was added, and they were mixed thoroughly using a pestle and mortar. The reaction mixture was placed in air at room temperature with further occasional mixing. On completion of the reaction as monitored by TLC (hexane:ethyl acetate $=4{:}1$, v/v), the product was extracted into $2\times 20\,cm^3$ of CH_2Cl_2. The removal of solvent under reduced pressure afforded the pure disulfide.

General Procedure for the Conversion of Thiols to Disulfides by Quinolinium Fluorochromate in Acetonitrile

To a solution of 1 mmol of thiol in $10\,cm^3$ of acetonitrile, 0.249 g of *QFC* (1 mmol) were added and the mixture was stirred at room temperature. After the completion of the reaction (TLC), the reaction mixture was filtered and the solid material was washed with $20\,cm^3$ of acetonitrile. The filtrate was evaporated and the resulting crude material was either recrystallized from methanol or subjected to a silica-gel plate (hexane:ethyl acetate $=4{:}1$, v/v) to afford the pure product.

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