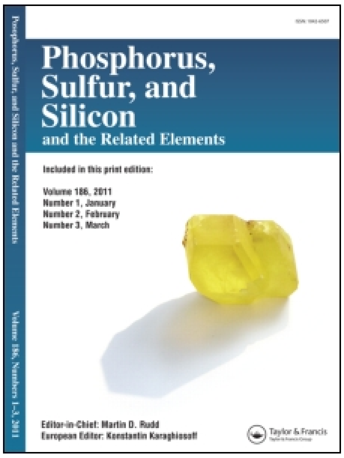

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$Fe(HSO_4)_3$ and $Fe(HSO_4)_3$/DMSO as Efficient, Heterogeneous, and Reusable Catalyst Systems for the Oxidative Coupling of Thiols

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$Fe(HSO_4)_3$ and $Fe(HSO_4)_3$/DMSO as Efficient, Heterogeneous, and Reusable Catalyst Systems for the Oxidative Coupling of Thiols

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$Fe(HSO_4)_3$ has been used as a heterogeneous, efficient, and recyclable catalyst in ethanol for the selective oxidation of thiols to their corresponding disulfides. The same results were obtained under identical conditions using catalytic amounts of $Fe(HSO_4)_3$ in the presence of DMSO. Different types of aliphatic, aromatic, and heteroaromatic thiols have been used in the reaction, and in all cases the products were obtained in good to excellent yields.

KEYWORDS Disulfide; DMSO; $Fe(HSO_4)_3$; heterogeneous; oxidation; thiol

INTRODUCTION

The oxidative coupling of thiols to disulfides under mild conditions is of practical importance in synthetic chemistry[1] and biochemistry.[2] Disulfides have found industrial applications as vulcanizing agents[3] and are important synthetic intermediates with many applications in organic synthesis. They can be used to prepare sulfinyl and sulfenyl compounds.[4] In biological systems, thiols are oxidized by flavins, cytochromes, and dehydroascorbic acid to control the cellular redox potential and prevent oxidative damage.[5] Recently, we have reported[6] a new application of disulfides in regioselective ring opening of epoxides to halohydrins with elemental halogens. Thiols can be easily over-oxidized and, therefore, extensive studies have been carried out to develop controlled conditions to disulfide preparation[7] such as bromine,[8] potassium dichromate,[9] Sm/$BiCl_3$,[10] potassium permanganate/copper(II)

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sulfate,[11] hydrogen peroxide in trifluoroethanol,[12] tungstate sulfuric acid,[13] I_2/DMSO,[14] HMDS/DMSO,[15] $MoO_2Cl_2(dmso)_2$,[16] and Mn(III) Schiff-base complex.[17] Enzymatic[18] and electrochemical[19] methods are also known to perform this oxidative transformation. However, most of these methods suffer from one or more disadvantage, such as long reaction times; difficult workup; lack of general applicability to thiol substrates bearing alkyl, aryl, and heteroaromatic moieties; formation of over-oxidation products leading to lower yields; or use of stoichiometric excess amounts of the expensive, rare, or toxic reagents for successful oxidation. Thus, there is still a need to develop a simple, mild, clean, and efficient oxidative method that would produce the target disulfides in high yields without complicated workup procedures.

Recently, ferric hydrogensulfate has emerged as a promising solid acid catalyst for acid catalyzed reactions, such as the Schmidt reaction,[20] functional group protections,[21,22] and Friedel–Crafts acylation.[22] We wish to report an efficient and simple method for oxidative coupling of thiols into the corresponding disulfides using molecular oxygen and/or DMSO catalyzed by $Fe(HSO_4)_3$ under mild conditions. In this regard, molecular oxygen is considered as an ideal "green" oxidant due to its strength and lack of toxic byproducts.

RESULTS AND DISCUSSION

$Fe(HSO_4)_3$ has the special advantages of ferric salts such as its insolubility in organic solvents, and this makes its recovery very convenient. It can be easily prepared from commercially available starting materials, stored and used after several months, and can be treated with supports and co-catalysts leading to a wide variety of reactions.

In order to determine the most appropriate reaction conditions and evaluate the catalytic efficiency of $Fe(HSO_4)_3$, initially a model study was carried out on the synthesis of diphenyl disulfide **(2a)** for optimization studies (Scheme 1). Among the tested solvents at different temperatures to facilitate the transformation of **(1a)**, ethanol was the most effective and gave the best conversion and highest yield in 45 min at room temperature (Table I, entry 9). The ferric hydrogenesulfate was easily recovered and reused for the next set of oxidation reactions without significant decrease in activity even after five runs (Table I, entries 9–13).

Further, when the oxidative coupling of thiophenol was carried out using a different amount of $Fe(HSO_4)_3$, the reaction was found to reach completion faster with an increase in amount of $Fe(HSO_4)_3$ up to 1 mmol (Table I, entries 9, 14, and 15). However, the oxidation of thiol in

$$\underset{1\text{ mmol}}{2\,\mathrm{ArSH}} \xrightarrow[\substack{\mathrm{DMSO,\ X\ mmol} \\ \mathrm{Solvent\ (5\ ml),\ rt}}]{\mathrm{Fe(HSO_4)_3,\ X\ mmol}} \mathrm{ArSSAr}$$

1a) Ar = Ph
1b) Ar = o-NH_2Ph

2a) Ar = Ph
2b) Ar = o-NH_2Ph

SCHEME 1

the absence of catalyst did not occur even under extension of reaction time to several days, and unreacted thiol was completely recovered (Table I, entry 16).

Interestingly, it was found that even 10 mol% $Fe(HSO_4)_3$ is an efficient catalyst when the reaction was carried out in the presence of dimethylsulfoxide and gave exclusively **(2a)** in 91% yield in 1.5 h (Table I, entry 17). Then we examined the same oxidation reaction of *o*-amino thiophenol **(1b)** under a catalytic amount of catalyst (0.1 mmol) in the presence of different amounts of DMSO at room temperature (Table I,

TABLE I Optimization of the Oxidative Coupling Reaction on Thiols by $Fe(HSO_4)_3$

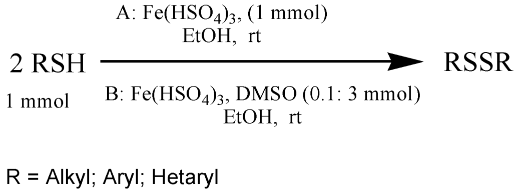
Entry	Substrate	$Fe(HSO_4)_3$ (mmol)	DMSO (mmol)	Solvent, Temperature (°C)	Time (h)	Yield (%)[a]
1	**1a**	1	0	CH_2Cl_2, 25	4	41
2	**1a**	1	0	CH_3CN, 25	2	45
3	**1a**	1	0	THF, 25	1.5	80
4	**1a**	1	0	n-Hexane, 25	5	35
5	**1a**	1	0	CH_3OH, 25	1	89
6	**1a**	1	0	C_2H_5OH/H_2O (50%), 25	1.2	87
7	**1a**	1	0	C_2H_5OH, 0	5.5	37
8	**1a**	1	0	C_2H_5OH, 55	0.4	80
9	**1a**	1	0	C_2H_5OH, 25	0.75	95
10[b]	**1a**	1	0	C_2H_5OH, 25	0.5	92
11[c]	**1a**	1	0	C_2H_5OH, 25	0.8	94
12[d]	**1a**	1	0	C_2H_5OH, 25	0.9	92
13[e]	**1a**	1	0	C_2H_5OH, 25	1	90
14	**1a**	0.5	0	C_2H_5OH, 25	2.5	73
15	**1a**	0.1	0	C_2H_5OH, 25	6.5	50
16	**1a**	0	0	C_2H_5OH, 25	7	0
17	**1a**	0.1	3	C_2H_5OH, 25	1.5	91
18	**1b**	0.1	3	C_2H_5OH, 25	0.58	96
19	**1b**	0.1	2	C_2H_5OH, 25	0.9	86
20	**1b**	0.1	1	C_2H_5OH, 25	1.6	85

[a] Isolated yields.

[b–e] Refer to the recycling of catalyst in new subsequent runs.

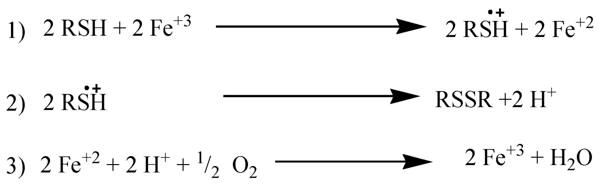
Entries 18–20). It was found that the optimum reaction rate and yield could be achieved by using three equivalents of DMSO in a catalytic system (Table I, Entry 18).

In order to evaluate the generality of the process of oxidative coupling, various aliphatic, aromatic, and heteroaromatic thiols were then examined using the optimized reaction conditions, and in both selected approaches, the oxidation was performed in good to excellent yields. The general reaction is illustrated according to the Scheme 2, and the results are summarized in Table II.



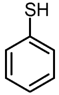
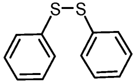
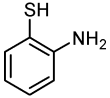
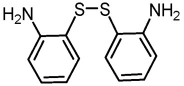
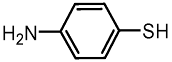
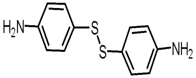
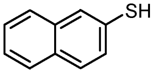
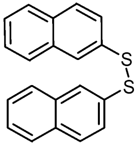
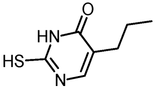
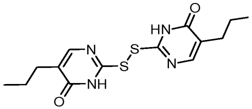
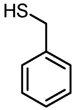
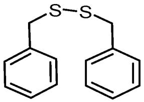
SCHEME 2

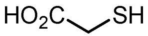
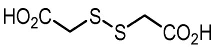
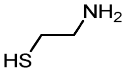
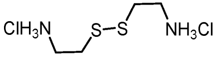
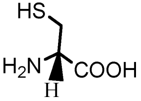
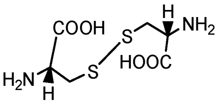
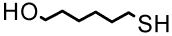
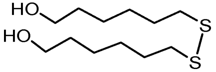
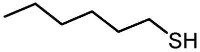
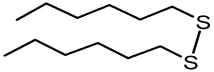
All reactions were performed in 8–480 min, and coupling of a variety of thiols confirmed the general applicability and practical utility of this method. All the reactions were carried out at room temperatures. As shown in Table II, the aromatic thiols having electron-donating substituents showed a high reactivity and selectivity (Table II, entries 1–4). Thiols with tautomeric thione and thiol forms had less reactivity than aromatic and aliphatic thiols (Table II, entry 5). Aliphatic thiols with short chains especially having an electron donating substituent (NH_2) in the chain showed a higher reactivity and selectivity in 8–60 min during the two reaction conditions (Table II, Entries 8–9) than long chains and those having carboxyl group (Table II, Entries 7, 10–11). The purity of the products was determined by ^{1}H NMR and IR spectra, which showed the exclusive formation of the corresponding disulfides whose structure was confirmed by melting point comparison. The suggested reaction mechanism is presented in Scheme 3. Although the exact mechanism of these transformations is still unclear, the catalytic system accelerated with DMSO probably involves the formation of an



SCHEME 3

TABLE II $Fe(HSO_4)_3$ and $Fe(HSO_4)_3$/DMSO Catalyzed Oxidative Coupling of Thiols to Disulfides

					Condition A		Condition B		Melting point (°C)	
Entry	Substrate		Product		Time (min)	yield[a,b] (%)	Time (min)	yield[a–c] (%)	Found	Lit [ref]
1		**1a**		**2a**	45	95	90	91	60–61	58–60 [23]
2		**1b**		**2b**	15	98	35	96	88–90	88 [24]
3		**1c**		**2c**	20	96	35	87	76–78	78 [24]
4		**1d**		**2d**	90	94	120	90	143–145	144 [25]
5		**1e**		**2e**	110	92	120	65	163	162 [26]
6		**1f**		**2f**	50	91	–	–	67–69	70 [24]

7		**1g**		**2g**	60	57	–	–	58–60	62 [27]
8		**1h**		**2h**	8	91	10	89	206(dec)	206(dec) [28]
9		**1i**		**2i**	25	92	60	85	256–257(dec)	257–259 [26]
10		**1j**		**2j**	480	81	360	75	45	45 [24]
11		**1k**		**2k**	120	80	180	60	oil	oil 71–73 [29]

[a] Isolated yields.

[b] All reactions were carried out at room temperature.

[c] All reactions were carried out under catalytic amounts of $Fe(HSO_4)_3$ in the presence of DMSO.

intermediate Fe(IV) or Fe(V) in the presence of dissolved oxygen in ethanol.

In conclusion, the results indicate that ferric hydrogene sulfate is an efficient and reusable heterogeneous catalyst for the oxidative coupling of thiols to disulfides. It has the capacity to be treated by other types of co-oxidants such as DMSO to operate more efficiently. Simplification of handling procedure; fewer byproducts; green chemistry; availibility, stability, and cheapness of catalyst; and clean workup with high yields make these methods as useful methodology for practical synthesis.

EXPERIMENTAL

All materials and solvents were obtained from Merck chemical company (Germany) and Fluka (Switzerland). Melting points were determined in open capillary tubes in an Electrothermal IA 9000 melting point apparatus. IR spectra were recorded on a Shimadzu IR 470 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker-100 MHz instrument using tetramethylsilane (TMS) as an internal standard. Ferric hydrogensulfate was prepared according to previously reported procedure.[20]

General Procedure for the Selective Oxidative Coupling of Thiols to Disulfides Catalyzed by $Fe(HSO_4)_3$

A mixture of thiol (1 mmol) and $Fe(HSO_4)_3$ (0.35 g, 1 mmol) in ethanol (5 mL) was stirred at room temperature until TLC indicated the reaction was complete. After the completion, the reaction mixture was filtered, and the organic solvent was then removed. The resulting residue was washed with a minimal volume of CH_2Cl_2:n-hexane (1:9) to give the crude product in high yield.

General Procedure for the Selective Oxidative Coupling of Thiols to Disulfides Catalyzed by $Fe(HSO_4)_3$/DMSO

A mixture of thiol (1 mmol), DMSO (3 mmol), and $Fe(HSO_4)_3$ (0.035 g, 0.1 mmol) in ethanol (5 mL) was stirred at room temperature until TLC indicated the reaction was complete. After the completion, the reaction mixture was filtered and the organic solvent was removed. The resulting residue was then dissolved in CH_2Cl_2 (5 mL), washed with water (2 × 10 mL), and dried with anhydrous Na_2SO_4. After solvent evaporation, the corresponding disulfide was obtained in high yield.

The products were characterized by comparison of their physical and spectral data with those reported in the literature.[23–29]

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