

Oxidative coupling of thiols to disulfides with iodine in wet acetonitrile[†]

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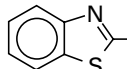
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Different types of thiols were oxidatively coupled to their disulfides with iodine in wet acetonitrile at room temperature and in excellent yields.

Keywords: thiol, disulfide, coupling, iodine

Thiols are among functional groups for which selective coupling to disulfides is of interest from both a biological¹ and a synthetic point of view.² This functional group can be easily over oxidised and therefore controlled oxidation to disulfides has been widely studied with different reagents,^{3–17} electrochemical¹⁸ and enzymatic¹⁹ methods. Recently, the using of 30% H₂O₂ in fluoroalcohols has been also applied for this transformation.²⁰ Although oxidative coupling of thiols with halogenes such as: I₂,²¹ I₂/HI,²² Br₂/aqueous KHCO₃,^{23a} Br₂/polyvinylpyridine complex^{23b} and Br₂²⁴ have been done, some of these methods give moderate yields and need precautions or long reaction times. In this context, we have already reported air oxygen in the presence of Fe(III)/NaI^{2b} could catalytically converted thiols to disulfides with excellent yields. In the line of our studies on this transformation, we now report an alternative procedure for this conversion. It was observed that the oxidative coupling of thiols occurred immediately with iodine in wet acetonitrile at room temperature (Table 1).

Table 1

RSH 1(a–l)		0.5 mol I ₂ , RT, Immediately Wet CH ₃ CN, 94–99%		RSSR 2(a–l)	
Entry	R groups	Entry	R groups		
1a	C ₆ H ₅	1g	n-Butyl		
1b	4-MeC ₆ H ₄	1h	Cyclohexyl		
1c	4-MeOC ₆ H ₄	1i	HOCH ₂ CH ₂		
1d	3-MeC ₆ H ₄	1j	Furfuryl		
1e	2-(H ₂ OC) ₆ H ₄	1k	2-Pyrimidyl		
1f	PhCH ₂	1l			

Reaction conditions were optimized with a set of experiments by performing the coupling reaction of thiophenol under different conditions (Table 2).

The results show that the coupling reaction of thiophenol could be done efficiently in wet acetonitrile, ethanol and ethanol-pyridine (1:1), but the rate of reaction in wet acetonitrile is higher than the others and we selected it as a suitable solvent for dimerisation of thiols. For formation of diphenyl disulfide, 0.5 mol equivalent of iodine is sufficient and the reaction is performed immediately at room temperature in an excellent yield (entry 6).

According to the reported method of using equimolar of iodine,²¹ the coupling reactions was not complete even under reflux and the obtained disulfides had moderate yields. But, in reinvestigation of this procedure we saw that the addition of a small amount of water as a co-solvent had an accelerating role and decreased the long reaction times to very short times. Then we studied the influence of water as a co-solvent with acetonitrile and other solvents and observed that a mixture of 1:5 of water-acetonitrile was a good mixture for excellent efficiency and very short reaction times. Therefore, we performed oxidative coupling of different aliphatic, aromatic and heteroaromatic thiols with 0.5 mol equivalent of iodine in a mixture of 1:5 of water-acetonitrile. All the reactions proceeded immediately at room temperature in quantitative yields (Table 3).

Various thiols (**1**) in the presence of 0.5 mol equivalent of I₂ converted to their disulfides (**2**) in a mixture of 1:5 of water-acetonitrile as a solvent. Aromatic thiols could be oxidised immediately to corresponding disulfides in quantitative yields. Thiophenol (**1a**), 4-methylthiophenol (**1b**), 4-methoxythiophenol (**1c**), 3-methylthiophenol (**1d**) exhibited a similar reactivity leading quickly to the disulfides **2a**, **2b**, **2c** and **2d** respectively with no detectable substituent influence.

Table 2 Oxidative coupling of thiophenol with I₂ under different reaction conditions^a

Entry	Molar ratio thiol/I ₂	Solvent	Time/h	Conversion/% ^b
1 ^c	1:0.5	CH ₃ CN	6	50
2 ^c	1:0.5	C ₂ H ₅ OH	2	35
3 ^c	1:0.5	C ₂ H ₅ OH-Pyridine	2	30
4	1:0.25	CH ₃ CN-H ₂ O (5:1)	4	40
5	1:0.4	CH ₃ CN-H ₂ O (5:1)	3	93
6	1:0.5	CH ₃ CN-H ₂ O (5:1)	Immediately	100
7	1:0.5	C ₂ H ₅ OH-H ₂ O (5:1)	0.17	100
8	1:0.5	C ₂ H ₅ OH-Pyridine-H ₂ O (2:2:1)	0.25	100

^aAll reactions were performed at room temperature. ^bConversions referred to TLC monitoring and isolated products.

^cThese reactions were performed in dry solvents.

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 3 Oxidative coupling of thiols to their disulfides with iodine in wet acetonitrile^a

Substrate	Product	Molar ratio I ₂ /Subs.	Yields/% ^b
1a	2a	0.5:1	99
1b	2b	0.5:1	95
1c	2c	0.5:1	98
1d	2d	0.5:1	99
1e	2e	0.5:1	97
1f	2f	0.5:1	98
1g	2g	0.5:1	94
1h	2h	0.5:1	94
1i	2i	0.5:1	94
1j	2j	0.5:1	97
1k	2k	0.5:1	99
1l	2l	0.5:1	98

^aAll reactions were performed immediately at room temperature in a mixture of 1:5 H₂O:CH₃CN. ^bYields referred to isolated products.

Under the same conditions 2-carboxythiophenol (**1e**) afforded the corresponding disulfide **2e** in 97% yield and steric hindrance at the α -position did not affect the rate of the reaction.

Benzylthiol (**1f**) and aliphatic thiols **1(g-i)** underwent oxidation with the same procedure to afford the corresponding disulfides **2f**, **2g**, **2h** and **2i** in quantitatively yields within very short times. The facile conversion of heteroaromatic thiols was demonstrated by the oxidation of furfurylthiol (**1j**), 2-pyrimidinethiol (**1k**) and 2-benzothiazolthiol (**1l**). Thus furfuryl thiol (**1j**) underwent oxidation with I₂ in wet acetonitrile to afford difurfuryl disulfide **2j** in 97% yield. 2,2'-Dipyrimidyl disulfide (**2k**) and 2,2'-benzothiazol disulfide (**2l**) were also obtained in near quantitative yields. In Table 3, we see that the efficiencies of the reactions are high and disulfides were obtained in 94–99% yields. Also, the rates of reaction were independent of the type of thiol or substituents and completed immediately. To show the advantageous of this procedure, we compared some of our results with those of reported methods (Table 4).

The results show that the oxidative couplings of thiols in wet acetonitrile with respect to the rate of reactions are very fast and the efficiency of reactions are higher or comparable with other methods. The simplicity, mild, neutral conditions and high efficiencies make iodine in wet acetonitrile a bench top method in organic synthesis for this transformation. In this method, there is no need for metal catalyst or expensive reagents and so this might be useful in large-scale synthesis.

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Experimental

All products were characterised by a comparison of their physical data with those of authentic samples (IR, ¹H NMR and MS). All yields referred to isolated products. TLC accomplished the purity determination of the substrates, products and reactions monitoring

over silica gel PolyGram SILG/UV 254 plates. Compounds **2a**²⁵, **2b**²⁶, **2c**^{3d}, **2d**²⁶, **2e**⁷, **2f**^{3d}, **2g**²⁷, **2h**²⁸, **2i**^{23a}, **2j**^{2b}, **2k**²⁹ and **2l**^{5f} are known.

Oxidative coupling of thiophenol to diphenyl disulfide with iodine; typical procedure: A round bottom flask equipped with magnetic stirrer is charged with thiophenol (10 mmol, 1.10 g) (**1a**) and a mixture of 1:5 of water-acetonitrile (30 ml). Then to the stirring solution, iodine (5 mmol, 1.27 g) was added at room temperature and the reaction was immediately completed. Completion of the reaction was monitored by TLC. After that, a solution of 1% aqueous sodium thiosulfate (30 ml) was added and the mixture was stirred on to decolourisation of brown–yellow reaction mixture. The mixture was then extracted with CH₂Cl₂ (3×40 ml) and dried over anhydrous Na₂SO₄. The organic solution was evaporated to dryness and the residue was chromatographed on a short column of silica gel using CCl₄ as eluent. The pure diphenyl disulfide (**2a**) was obtained as colourless crystals (1.08 g, 99% yield). m.p. 59–60°C (lit.²⁵ 60°C), IR (KBr): ν /cm⁻¹ 3051, 1572, 1475, 1435, 734, 688, 459; ¹H NMR (CDCl₃): δ 7.64–7.5 (m, 4H), 7.43–7.21 (m, 6H).

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Table 4 Comparison of oxidative coupling of thiols to their disulfides with iodine in wet acetonitrile and some other reported reagents

Entry	Thiol	Disulfide	Molar ratio (reag./subs.)/Time/min/Yields/%					
			I	II ²⁴	III ^{23a}	IV ^{2b}	V ¹⁷	VI ¹⁵
1	1a	2a	0.5(1m)(99)	0.5 ^{a,b}	0.5 ^a (100)	(15)(97) ^c	0.32(33)(89)	0.2(10)(98)
2	1b	2b	0.5(1m)(95)	0.5 ^{a,b}	0.5 ^a (100)	(30)(98) ^c	0.32(32)(78)	–
3	1f	2f	0.5(1m)(98)	0.5 ^{a,b}	0.5 ^a (98)	(10)(99) ^c	–	0.2(5)(96)
4	1g	2g	0.5(1m)(94)	0.5 ^{a,b}	0.5 ^a (96)	(7)(97) ^c	0.32(21)(98)	0.2(10)(92)
5	1h	2h	0.5(1m)(94)	0.5 ^{a,b}	–	(20)(98) ^c	–	0.2(130)(95)
6	1j	2j	0.5(1m)(97)	–	–	(12)(96) ^c	–	0.2(3)(93)

I) I₂ / wet acetonitrile; II) Br₂; III) Br₂/KHCO₃; IV) Air Oxygen/FeCl₃/NaI; V) KMnO₄/CuSO₄ (gr); VI) Cu(NO₃)₂·3H₂O

^aReaction was completed during addition of the reagent. ^bQuantitatively. ^cMolar ratio: Air oxygen / 0.1/ 0.2 1m means immediately.

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