

Catalytic oxidation of thiols to disulfides using iodine and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in graphite

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Abstract—A very simple procedure for the efficient oxidation of thiols to disulfides catalyzed by $\text{I}_2/\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in graphite and ethyl acetate as the solvent, in an open system at room temperature is described. The reaction proceeds cleanly under mild conditions and was performed with aromatic, aliphatic, and heterocyclic thiols.

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The conversion of thiols to the corresponding disulfides is an important reaction in biological and chemical processes.¹ Reagents such as cerium(IV) salts,² transition metal oxides,³ molecular oxygen,⁴ nitric oxide,⁵ halogens,⁶ sodium perborate,⁷ H_2O_2 ,⁸ solvent free permanganate,⁹ 2,6-dicarboxypyridinium chlorochromate,¹⁰ 1,3-dibromo-5,5-dimethylhydantoin,¹¹ among others have been utilized for oxidation of thiols to disulfides.¹²

In the course of studies on some reaction of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and iodine, we have observed the oxidative dimerization of thiols. Our continuing interest in the synthesis and applications of organochalcogenium chemistry¹³ prompted us to examine and expand the scope of this reaction. A set of experiments were performed to find the best conditions for the oxidation, using thiophenol as a model compound. A series of different supports and solvents were examined and results are presented in Tables 1 and 2, respectively. By the results described in Table 1, one can observe that the use of graphite is a very convenient solid support for the reaction, performed without any solvent. Graphite has been emerging as a very convenient support for a series of synthetic transformations.¹⁴ However, as the reaction under dry media condition was not efficient, with 83% conversion (GC analysis) in graphite after 9 h, we turned our attention to the use of a solvent. We observed moderate yields using EtOH and MeOH (Table 2, entries 2

and 3), while optimal results were achieved using MeCN and AcOEt (Table 2, entries 1 and 8). Gratifyingly, the use of AcOEt, an inexpensive and environmentally benign solvent, resulted in the disulfide in quantitative yield.

Our next attention was devoted to minimum amounts of iodine and CeCl_3 to have a good reaction rate. We observed that the amounts of both reagents can be reduced substantially, to 5 and 10 mol % (Table 2, entry 8), respectively. It is worthy to note the effect of iodine and CeCl_3 on the oxidation. Under the standard conditions, the absence of iodine or CeCl_3 reduces the conversion rates substantially (Table 2, entries 6 and 7).

Careful analysis revealed that the optimum conditions for this oxidation reaction were found to be the use of ethyl acetate and graphite, under catalysis of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (10 mol %) and I_2 (5 mol %), at room temperature and air atmosphere (Scheme 1). A detailed study was performed with aliphatic, aromatic, and heterocyclic thiols, showing the generality of the method. For most examples, very high yields were obtained, the exceptions

Table 1. Oxidation of thiophenol in dry media at different supports

Entry	Support ^a	Time (h)	Conversion (% GC)
1	—	9	11
2	SiO_2	9	27
3	PEG400	9	17
4	Graphite	9	83

^a PhSH (1 mmol), support (0.3 g), I_2 (1 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1 mmol).

Keywords: Thiols; Disulfides; Oxidation; Cerium chloride; Iodine; Graphite.

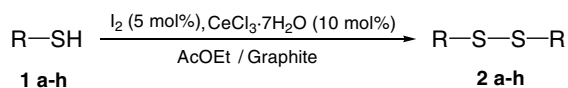
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Table 2. Oxidative coupling of thiophenol supported in graphite under different solvent

Entry	Solvent ^a	Time (h)	I ₂ (equiv)	CeCl ₃ ·7H ₂ O (equiv)	Conversion (% GC)
1	MeCN	1	1	1	100
2	MeOH	14	1	1	57
3	EtOH	14	1	1	44
4	AcOEt	1	1	1	100
5	AcOEt	1	0.08	0.5	100
6	AcOEt	1	—	0.5	39
7	AcOEt	1	0.08	—	75
8	AcOEt	1	0.05	0.1	100
9	AcOEt	14	0.05	0.1	33 ^b

^a Solvent (1 mL/mmol), PhSH (1 mmol), graphite (0.3 g/mmol).









^b Reaction performed without graphite.

**Scheme 1.**

being entries 7 and 8, Table 3, mostly related to difficulty of isolation of the corresponding disulfide, since the reactions demanded the use of water as a co-solvent and adjust of pH.¹⁵ The oxidation reaction can be easily scaled-up with similar results.

In conclusion, the method described is very simple and efficient for coupling of thiols, using catalytic amounts of iodine and CeCl₃ in the inexpensive graphite as solid support. The method is applicable to a wide variety of thiols, being a useful alternative of the existing methodologies.

Table 3. Catalytic oxidation of thiols to disulfides

Entry	Thiol	Time (h)	Product	Yield ^a (%)	Mp/bp °C (Lit.)
1		1.5	2a^b	97	195 (194/760 mmHg) ¹⁶
2		0.8	2b^b	98	30–32 (32) ¹⁷
3		1.0	2c^b	99	57–58 (59–60) ¹⁸
4		1.0	2d^b	97	69–70 (70–71) ^{6b}
5		0.9	2e^b	98	42–43 (43–44) ¹⁹
6		1.0	2f^b	96	72–73 (73–74) ²⁰
7		2.5	2g^c	74	167–169 (168–170) ²¹
8		3.5	2h^c	77	243–245 dec (>240 dec) ²²

^a Isolated yield.

^b Reaction in AcOEt (Method A).

^c Reaction in AcOEt/H₂O (Method B).

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15. *General procedures for the oxidation. Method A:* A round bottom flask was charged with ethyl acetate (1 mL), graphite (0.3 g), I₂ (0.05 mmol), and CeCl₃·7H₂O (0.1 mmol). The mixture was stirred for 10 min, then the thiol (1 mmol) was added. The reaction was monitored by TLC or GC. After completion of the reaction, ethyl acetate (25 mL) was added and the reaction mixture was washed with satd aq Na₂S₂O₃, water, and dried over MgSO₄. The solvent was removed and the residue purified by recrystallization or silica gel chromatography. *Method B:* Ethyl acetate (1 mL) was added to a solution of thiol (1 mmol) in water (1 mL) and the pH was adjusted to 10 with 1 M aq NaOH. Then graphite (0.3 g), I₂ (0.05 mmol), and CeCl₃·7H₂O (0.1 mmol) were added and the reaction was monitored by TLC or GC until completion, and the reaction mixture was evaporated to dryness. Product **2g** was extracted and purified as described in Method A. Product **2h** was recrystallized from water.
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