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Europhtal (8020) efficiently catalyzes the aerobic oxidation of in situ generated thiols to symmetric disulfides (disulfanes)

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ABSTRACT

Efficient, odorless and scalable synthetic protocols have been introduced for the preparation of symmetric alkyl disulfides by treatment of the corresponding organic halides with thiourea and $NaHCO_3$ in the presence of commercially available Europhtal catalyst (8020) in both H_2O and poly ethylene glycol (PEG-200) media at 80–90 °C. Structurally diverse primary, secondary, allylic and benzylic halides were examined successfully whereas, the result with *tert*-butyl bromide was not satisfactory. Also, another procedure has been introduced for achieving symmetric aryl disulfides in high yields by reacting aryl halides, thiourea and $NaHCO_3$ in PEG-200 at 115–120 °C using CuI along with Europhtal catalysts. The results showed that the aerobic oxidation of in situ generated thiols proceeded efficiently in the presence of Europhtal catalyst giving the symmetric disulfide without contamination by symmetric sulfide side-product.

1. Introduction

Organic disulfides are important molecules in biological, industrial and chemical processes. Disulfide linkage plays an important role in maintaining secondary and tertiary structures in proteins [1], DNA-cleaving [2], synthesis of drug delivery molecules [3], synthesis of self-assembled monolayers on a metal surface [4,5] and vulcanization of polymers [6,7]. In organic reactions, disulfides have been used for sulfenylation of a variety of organic substrates including indoles [8–12], benzoxazoles [13], benzothiazoles [14–16], aldehydes [17–20], nitroalkanes [21,22], 1,3-dicarbonyl compounds [23–25], ketones [26,27], phosphonates [28–30], alkyl [31–37], aryl [38–42], vinyl- [43–45], and acyl halides [46,47], epoxides [48–52], Michael acceptors [53–55], allenes [56], alkenes [57–63], alkynes [64–66] and carbon monoxide [67–69].

Symmetrical disulfides can be obtained from different organic substrates including Bunte salts, sulfonyl chlorides, aromatic compounds, alkynes, alkenes, organic thiocyanates, alkyl halides and thiiranes [70]. Traditionally, symmetric disulfides are synthesized by oxidation of the corresponding thiols using many oxidizing reagents [70]. Also, the aerobic oxidation of thiols has long been recognized for the preparation of symmetric disulfides. It is not quite efficient in most cases and needs an effective catalyst. In this context, the aerial oxidation of thiols to disulfides has been reported with flavin [71], cesium fluoride–celite [72], silica chloride [73], anhydrous potassium phosphate [74], graphite oxide [75], hydrotalcite clay [76], iron [77,78], bismuth tungstate nanoparticles [79], photocatalytic conditions [80,81], hierarchical mesoporous Mn-MFi zeolite nanoparticles [82], manganese octahedral molecular sieve [83], copper nanoparticles supported on diamond nanoparticles [84], heterogeneous gold catalysts [85], NiO/MgO/SiO_2 supported cobalt(II) tetrasulfophthalocyanine, [86] manganese(III) schiff-base complex, [87] cobalt-iron magnetic composites [88], cobalt phthalocyanine [89], trichlorooxyvanadium [90], silica-supported cobalt(II) tetrasulfophthalocyanine [91], iron metal-organic frameworks [92] and under ball-milling in the absence of any catalyst [93]. The aerial oxidation of thiols to disulfides using commercial sulfonated cobalt phthalocyanine complexes such as Europhtal sweetening catalysts (Fig. 1) is industrially applied to remove offensive mercaptans from LPG and lighter petroleum fractions.

Besides, symmetrical disulfides could be synthesized by oxidation of thiols in situ generated from the reaction of alkyl halides and a sulfur-transfer reagent such as thiourea (Scheme 1) [95–99].

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0022-328X/

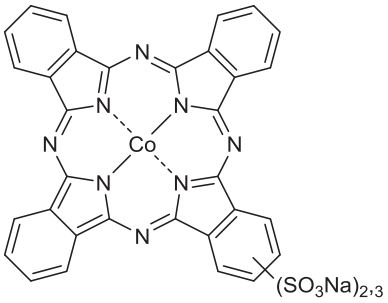


Fig. 1. Structural formula of Europhtal catalyst [94].

One of the main advantages of such reactions is that they are free from the thiolic foul-smells. In this strategy, the intermediate *S*-alkylisothiouronium salt is produced primarily by reacting alkyl halide with thiourea which subsequently undergoes basic hydrolysis to generate the corresponding thiol moiety. This moiety can react with an alkyl halide molecule to produce the corresponding symmetric sulfide or can react with applied oxidant to produce the corresponding symmetric disulfide. To obtain symmetric disulfide without contamination with symmetric sulfide, the thiol moiety should be oxidized before it gets a chance to react with a free alkyl halide molecule. As another trouble, many oxidizing reagents can destroy thiourea or can convert a part of thiol to side products. Hence, the selection of a proper oxidant is crucial to achieve disulfides in high yields. Up to now, MnO_2, $BaMnO_4$ [95,96], elemental sulfur [97], CCl_4 [98], and dimethyl sulfoxide (DMSO) in conjunction of hexamethyldisilazane (HMDS) [99] are successfully applied for this purpose.

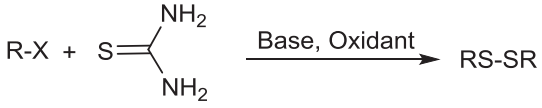
2. Experimental

2.1. Catalyst information

Europhtal catalyst solution additive 8020, an industrial catalyst, containing both bis- and tris-sulfonated cobalt phthalocyanine complexes (Fig. 1), supplied by the Europhtal company (Cavaillon, France) was used in this study. After heating of the solution for 2 h in an oven at 100 °C, a dark-blue solid residue sticking to the beaker floor was obtained in 0.344 g/mL.

2.2. General procedure for conversion of alkyl halides to disulfides in PEG

In a round-bottom flask (25 mL) equipped with a condenser, Europhtal (8020) catalyst solution (0.07 mL) was added to a mixture of an alkyl halide (2.0 mmol), thiourea (2.2 mmol), H_2O (0.1 mL), and $NaHCO_3$ (3.0 mmol) in PEG 200 (1 mL) and the mixture was stirred magnetically in an oil bath at 80–90 °C. The stirring was continued under such conditions up to 2 h after the complete consumption of the starting halide. Next, the mixture was diluted with water (0.5 mL) and extracted with 1:2 *n*-hexane/EtOAc (3 × 1 mL). The organic layers were decanted, combined, and concentrated to yield the crude product, which was further purified by silica gel chromatography, using *n*-hexane as eluent.



Scheme 1. Synthesis of disulfides by oxidation of in situ generated thiols.

2.2.1. Typical scale-up procedure for the conversion of n-butyl bromide into disulfide in PEG-200(Table 1, entry 5)

In a round-bottom flask (250 mL) equipped with a condenser, a solution of *n*-butyl bromide (30.0 mmol, 4.111 g), thiourea (33.0 mmol, 2.512 g), H_2O (1.5 mL) and Europhtal (8020) catalyst solution (1.05 mL) in PEG-200 (15 mL) was prepared. Then, $NaHCO_3$ (45.0 mmol, 3.780 g) was added to this solution and the resulting mixture was stirred magnetically in an oil bath at 80–90 °C. The starting halide was consumed within 1.5 h, however, the reaction mixture was stirred under that conditions for 3.5 h to ensure the completion of the reaction. Afterwards, the mixture was diluted with H_2O (7.5 mL) and extracted with 1:2 *n*-hexane/EtOAc (4 × 10 mL). The organic layers were decanted, combined, and concentrated. The crude product was purified by silica gel chromatography, using *n*-hexane as eluent to provide dibutyl disulfide. in 88% (2.354 g) yield.

2.3. General procedure for preparation of disulfides from alkyl halides in SDS micellar solution

To a micellar solution of SDS (1 mL H_2O + 0.1 mmol SDS) in a round-bottom flask (25 mL) equipped with a condenser, an alkyl halide (2.0 mmol), thiourea (2.2 mmol), Europhtal (8020) catalyst solution (0.07 mL) and $NaHCO_3$ (3.0 mmol) were added. The resulting mixture was stirred magnetically in an oil bath at 80–90 °C up to 2 h after the complete consumption of the starting halide. Thereafter, the mixture was directly extracted with EtOAc (3 × 1 mL). The upper layers were combined, and concentrated. The crude product underwent silica gel chromatography with *n*-hexane to provide the desired symmetric disulfide in pure form.

2.3.1. Typical scale-up procedure for the preparation of dibutyl disulfide from n-butyl bromide in SDS micellar solution (Table 1, entry 5)

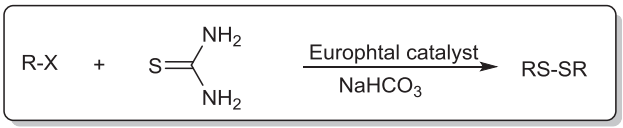
To a micellar solution of SDS (15 mL H_2O +0.75 mmol SDS), in a round-bottom flask (250 mL) equipped with a condenser, thiourea (33.0 mmol, 2.512 g), *n*-butyl bromide (30.0 mmol, 4.111 g), Europhtal catalyst (1.15 mL), and $NaHCO_3$ (45.0 mmol, 3.780 g) were added. The resulting mixture was stirred magnetically in an oil bath at 80–90 °C. The starting halide was consumed within 5 h however, the stirring was continued under such conditions for further 2 h. Next, the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were decanted, combined, dried over Na_2SO_4, filtered and concentrated to yield the crude product, which was further purified by silica gel column chromatography, using *n*-hexane to provide the desired product in 2.300 g (86% yield).

2.3.1.1. Didecyl disulfide (Table 1, entry 1). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 2.63 (t, J = 7.3 Hz, 4H), 1.76–1.61 (m, 4H), 1.21 (broad band, 28H), 0.82 (t, J = 6.2, 6H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 39.2, 31.9, 29.6, 29.5, 29.3, 29.3, 29.2, 28.5, 22.7, 14.1; Anal. Calcd for $C_{20}H_{42}S_2$: C, 69.29; H, 12.21; S, 18.50%. Found: C, 69.40; H, 12.23; S, 18.37%.

2.3.1.2. Dioctyl disulfide (Table 1, entry 3). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 2.61 (t, J = 7.3 Hz, 4H), 1.66–1.54 (m, 4H), 1.30–1.21 (broad band, 20H), 0.81 (t, J = 6.2, 6H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 39.2, 31.8, 29.2, 29.2, 29.1, 28.5, 22.6, 14.1; Anal. Calcd for $C_{16}H_{34}S_2$: C, 66.14; H, 11.79; S, 22.07%. Found: C, 66.07; H, 11.81; S, 22.12%.

2.3.1.3. Dibutyl disulfide (Table 1, entry 5). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 2.69 (t, J = 7.4, 4H), 1.71–1.66 (m, 4H), 1.48–1.40 (m, 4H), 0.93 (t, J = 7.3, 6H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 39.3, 31.7, 22.0, 14.0. Anal. Calcd for $C_8H_{18}S_2$: C, 53.88; H, 10.17; S,

Table 1
One-pot transformation of alkyl halides into symmetric disulfides.



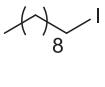
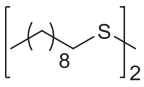
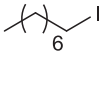
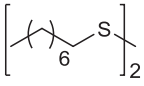
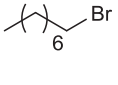
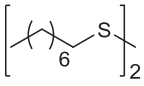
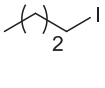
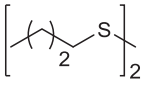
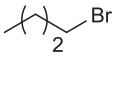
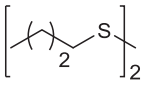
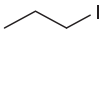
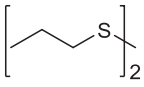
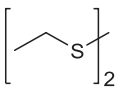
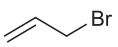
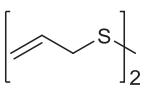
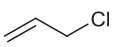
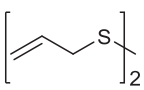
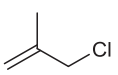
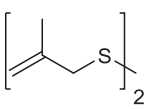
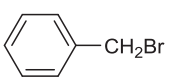
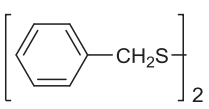
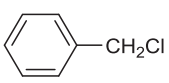
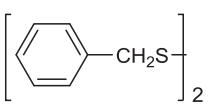
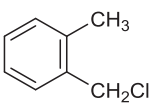
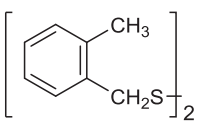
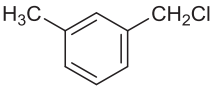
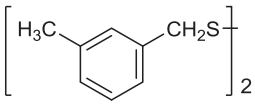
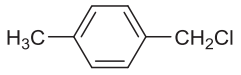
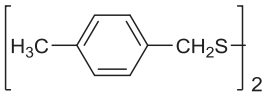
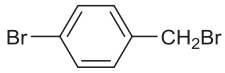
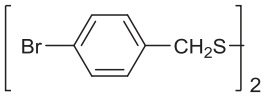
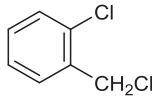
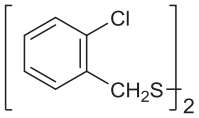
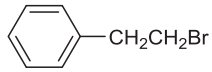
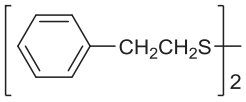
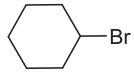
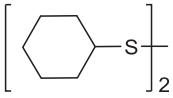
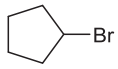
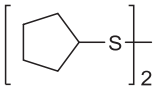
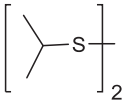
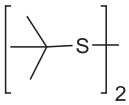
Entry	Alkyl halide	Product	in PEG[a]		in SDS micellar media[b]	
			Time (h)[c]	Yield (%)	Time (h)[c]	Yield (%)
1			2	90	4	86
2			2	93	4	88
3			3	88	6	86
4			1	88	2	85
5			1.5	88	5	86
6			1	86	2	86
7[d]			5	87	24	–
8[d]			5	90	8	85
9[d]			7	88	16	83
10[d]			7	88	16	86
11			0.5	91	0.5	88
12			0.5	90	0.5	90
13			0.5	89	0.5	85
14			0.5	89	0.5	88

Table 1 (*continued*)

Entry	Alkyl halide	Product	in PEG[a]		in SDS micellar media[b]	
			Time (h)[c]	Yield (%)	Time (h)[c]	Yield (%)
15			0.5	88	0.5	89
16			0.5	89	0.5	85
17			0.5	91	0.5	86
18			2	87	6	86
19			10	88	24	trace
20			10	87	24	trace
21[d]			36	83	72	–
22[e]			24	˂20	72	–

[a] Reaction conditions: alkyl halide (2 mmol), thiourea (2.2 mmol), $NaHCO_3$ (3 mmol), Europhtal (8020) catalyst solution (0.07 mL), H_2O (0.1 mL), PEG (1 mL), 80–90 °C.
[b] Reaction conditions: alkyl halide (2 mmol), thiourea (2.2 mmol), $NaHCO_3$ (3 mmol), Europhtal (8020) catalyst solution (0.07 mL), H_2O (1 mL), SDS (0.1 mmol), 80–90 °C.
[c] Time refers to consumption of the starting alkyl halide.
[d] Reaction was conducted at 35–40 °C using Na_2CO_3 instead of $NaHCO_3$.
[e] Reaction was conducted at 70 °C.

35.95. Found: C, 53.73; H, 10.29; S, 35.98.

2.3.1.4. Bis(2-methyl-2-propenyl) disulfide (Table 1, entry 10). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 4.89–4.80 (m, 4H), 3.22 (s, 4H), 1.76 (s, 6H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 140.7, 114.9, 46.4, 20.9; Anal. Calcd for $C_8H_{14}S_2$: C, 55.12; H, 8.09; S, 36.79%. Found: C, 55.03; H, 8.06; S, 36.91%.

2.3.1.5. Dibenzyl disulfide (Table 1, entry 11). White crystal powder, M.p. 68–70 °C (Lit. 68–70 °C) [100]; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 10H), 3.61 (s, 4H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 138.6, 130.7, 129.7, 128.7, 44.4; Anal. Calcd for $C_{14}H_{14}S_2$: C, 68.25; H, 5.73; S, 26.02%. Found: C, 68.39; H, 5.76; S, 25.85%.

2.3.1.6. Bis(2-methylbenzyl) disulfide (Table 1, entry 13). Withe crystals powder; m.p.71–73 °C (Lit. 71–73 °C) [101]; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.26–7.13 (m, 8H), 3.67 (s, 4H), 2.38 (s, 6H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 135.8, 134.0, 129.5, 129.4, 126.7, 124.9, 40.5, 18.2. Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.37%. Found: C, 69.91; H, 6.55; S, 23.54%.

2.3.1.7. Bis(3-methylbenzyl) disulfide (Table 1, entry 14). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.30–7.07 (m, 8H), 3.62 (s, 4H), 2.39 (s, 6H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 138.1, 137.3, 130.2, 128.4, 128.2, 126.5, 43.3, 21.4. Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.37%. Found: C, 69.97; H, 6.77; S, 23.26%.

2.3.1.8. Bis(4-methylbenzyl) disulfide (Table 1, entry 15). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.05 (s, 8H), 3.52 (s, 4H), 2.25 (s, 6H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 137.2, 134.4, 129.4, 129.3, 42.7, 21.3; Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.37%. Found: C, 70.09; H, 6.58; S, 23.33%.

2.3.1.9. Bis(4-bromobenzyl) disulfide (Table 1, entry 16). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.35 (d, J = 8.3 Hz, 4H),7.00 (d, J = 8.3 Hz, 4H), 3.46 (s, 4H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 136.3, 131.7, 131.2, 121.5, 42.5; Anal. Calcd for $C_{14}H_{12}Br_2S_2$: C, 41.60; H, 2.99; S, 15.87%. Found: C, 41.66; H, 2.90; S, 15.93%.

2.3.1.10. Bis(2-chlorobenzyl) disulfide (Table 1, entry 17). Yellow crystals; m.p.70–72 °C (Lit. 74 °C) [102]; ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.40–7.18 (m, 8H), 3.79 (s, 4H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 135.0, 134.1, 131.6, 129.7, 128.9, 126.7, 41.1. Anal. Calcd for $C_{14}H_{12}Cl_2S_2$: C, 53.34; H, 3.84; S, 20.34%. Found: C, 53.44; H, 3.96; S, 20.19%.

2.3.1.11. Dicyclohexyl disulfide (Table 1, entry 19). Colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.69–2.61 (m, 2H) 2.03–1.97 (m, 4H) 1.80–1.72 (m, 4H) 1.63–1.55 (m, 2H) 1.34–1.14 (m, 10H); ^{13}C NMR (62.5 MHz, $CDCl_3$): 49.9, 32.8, 26.1, 25.7; Anal. Calcd for $C_{12}H_{22}S_2$: C, 62.55; H, 9.62; S, 27.83. Found: C, 62.70; H, 9.55; S, 27.75%.

2.3.1.12. Dicyclopentyl disulfide (Table 1, entry 20). Colorless oil: ^{1}HNMR (250 MHz, $CDCl_3$): δ 3.45–3.39 (m, 2H), 1.97–1.94 (m, 4H), 1.69–1.51 (m, 12H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 50.7, 32.9, 24.7; Anal. Calcd for $C_{10}H_{18}S_2$: C, 59.35; H, 8.97; S, 31.68%. Found: C, 59.51; H, 8.99; S, 31.50%.

2.3.1.13. DiisoPropyl disulfide (Table 1, entry 21). Colorless oil; ^{1}HNMR (250 MHz, $CDCl_3$): δ 1.30 (d, J = 6.9 Hz, 12H), 2.97 (m, 2H); ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 22.6, 41.4; Anal. Calcd for $C_6H_{14}S_2$: C, 47.95; H, 9.39; S, 42.66. Found: C, 47.85; H, 9.44; S, 42.71%.

2.4. General procedure for conversion of aryl halides to disulfides in PEG

In a round-bottom flask (25 mL) equipped with a condenser, Europhtal (8020) catalyst solution (0.07 mL) was added to a mixture of an aryl halide (2.0 mmol), thiourea (2.2 mmol), H_2O (0.1 mL), CuI (20 mol%, 0.076 g) and $NaHCO_3$ (3.0 mmol) in PEG 200 (1 mL). The mixture was stirred magnetically in an oil bath at 115–120 °C. After consumption of aryl halide, the mixture was diluted with water (0.5 mL) and extracted with 1:2 *n*-hexane/EtOAc (3 × 1 mL). The organic layers were decanted, combined, and concentrated to yield the crude product, which was further purified by silica gel chromatography, using *n*-hexane as eluent to provide the pure desired disulfide.

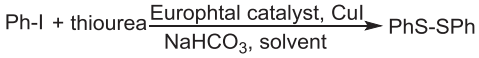
2.4.1. Diphenyl disulfide (Table 3, entry 1)

Withe crystals; m.p. 57–58 °C (Lit. 57 °C) [103]; ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.53–7.49 (m, 4H), 7.34–7.23 (m, 6H) ppm. ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 137.0, 129.4, 127.5, 127.1 ppm. Anal. Calcd for ($C_{12}H_{10}S_2$): C, 66.02; H, 4.62; S, 29.37. Found: C, 66.15; H, 4.52; S, 29.33%.

2.4.2. Di-p-tolyldisulfide (Table 3, entry 2)

Withe crystals; m.p. 43–45 °C (Lit. 42 °C) [103]; ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.36 (d, J = 8.6 Hz, 4H), 7.07 (d, J = 8.6 Hz, 4H), 2.28 (s, 6H) ppm. ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 137.4, 134.0, 129.8, 128.6, 21.1 ppm. Anal. Calcd for ($C_{14}H_{14}S_2$): C, 68.25; H, 5.73; S, 26.02. Found: C, 68.29; H, 5.83; S, 25.88%.

Table 2
Conversion of iodobenzene to diphenyl disulfide under various conditions.[a]



Entry	Solvent	CuI (mol%)	T (℃)	t (h)	Yield
1	H_2O	20	reflux	24	N R
2[b]	H_2O/SDS	20	reflux	24	N R
3	DMSO	20	120	24	trace
4	DMF	20	120	24	trace
5[c]	**PEG-200**	**20**	**120**	**12**	**91**
6	PEG-200	10	120	24	56
7	PEG-200	20	100	24	63

[a] Reaction Conditions: PhI (2 mmol), thiourea (2.2 mmol), $NaHCO_3$ (3 mmol), solvent (1 mL), Europhtal catalyst (0.07 mL).
[b] SDS (0.1 mmol, 5 mol%) was used.
[c] The best results.

2.4.3. Bis(4-methoxyphenyl)disulfide (Table 3, entry 3)

Withe crystals; m.p. 40–43 °C (Lit. 39 °C) [103]; ^{1}HNMR (250 MHz, $CDCl_3$): δ 7.34 (d, J = 8.8 Hz, 4H), 6.89 (d, J = 8.8 Hz, 4H), 3.83 (s, 6H) ppm. ^{13}CNMR (62.5 MHz, $CDCl_3$): δ 159.1, 132.8, 127.5, 114.7, 55.5 ppm. Anal. Calcd for ($C_{14}H_{14}O_2S_2$): C, 60.40; H, 5.07; S, 23.03. Found: C, 60.23; H, 5.17; S, 23.13%.

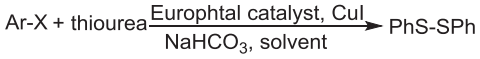
2.4.4. Bis(4-nitrophenyl)disulfide ((Table 3, entry 5)

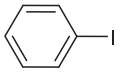
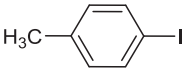
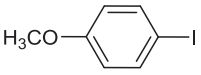
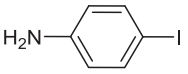
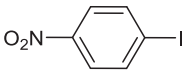
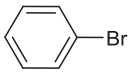
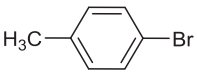
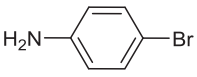
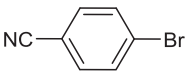
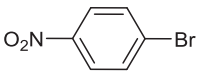
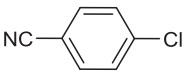
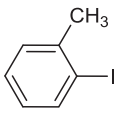
Withe crystals; m.p. 174–176 °C (Lit. 173–175 °C) [104]; ^{1}HNMR (250 MHz, $CDCl_3$): δ 8.16–8.10 (m, 4H), 7.44–7.40 (m, 4H) ppm. Anal. Calcd for ($C_{12}H_8N_2O_4S_2$): C, 46.75; H, 2.62; N, 9.09; S, 20.80. Found: C, 46.89; H, 2.73; N, 8.91; S, 20.65%.

3. Results and discussion

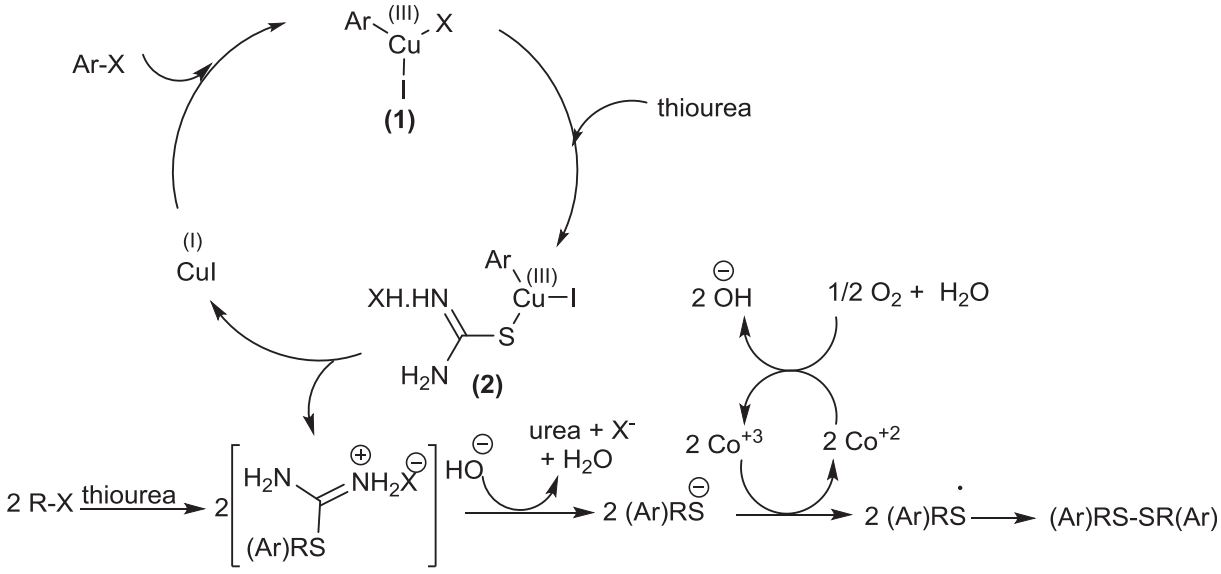
The development of a modified procedure using molecular

Table 3
One-pot synthesis of diaryl disulfides from aryl halides.



Entry	ArX	Time (h)	Yield (%)[b]
1		12	91
2		14	90
3		14	90
4		16	81
5		11	82
6		15	90
7		17	91
8		18	82
9		13	87
10		13	80
11		24	N R
12		24	N R

Reaction conditions: aryl halide (2 mmol), thiourea (2.2 mmol), CuI (0.4 mmol, 20 mol%), $NaHCO_3$ (3 mmol), Europhtal catalyst solution (0.07 mL), H_2O (0.1 mL), PEG (1 mL), 115–120 °C.



Scheme 2. A proposed reaction pathway.

oxygen as a mild, cheap and green oxidant is important from synthetic, economic and environmental points of view. Keeping this in mind, a set of reactions, using a mixture of octyl bromide (2.0 mmol), thiourea (2.2 mmol) and a common laboratory base (3.0 mmol) including $NaHCO_3$, Na_2CO_3, K_2CO_3, K_3PO_4, Et_3N and NaOH without using any catalyst in wet poly ethylene glycol (1 mL PEG-200 + 0.1 mL H_2O) were conducted in a 25 mL round-bottom flask under both air and oxygen atmosphere at r.t. and 80 °C for 12 h. The results were not satisfactory at all and an odorous mixture of dibenzyl sulfide and benzyl mercaptan was obtained. After that, the reaction in the presence of Europhtal (8020) catalyst at both 35–40 °C and 80–90 °C was tested. In the presence of 0.07 mL of commercial catalyst solution, the desired disulfide was obtained in 88% yield from the reaction of octyl bromide (2.0 mmol), thiourea (2.2 mmol) and $NaHCO_3$ (3.0 mmol) in wet PEG (1 mL PEG-200 + 0.1 mL H_2O) at 80–90 °C within 5 h. It should be noted that, the starting halide was completely consumed within 3 h but to ensure complete hydrolysis of the primary *S*-alkylisothiouronium salt intermediate to thiol followed by oxidation to disulfide, the stirring was continued under that conditions for further 2 h. No dibenzyl sulfide or free thiol was found in the reaction mixture during the reaction period and after completion of the reaction. The reactions extracts were also free from the thiol odor. The reproducibility of the reaction was proved by repeating the reaction five times. Notably, the same reaction conducted in a 75 mm × 10 mm test tube (instead of a 25 mL round-bottom flask) resulted a mixture of symmetric sulfide and disulfide due to reducing contact area with atmospheric oxygen. On the other hand, the use of Na_2CO_3 instead of $NaHCO_3$ under such conditions was not appropriate since it gave symmetric dibenzyl disulfide together with a little amount of dibenzyl sulfide. Also, by decreasing the catalyst quantity, the reaction gave symmetric sulfide in addition to the desired symmetric disulfide. The similar reaction at 35–40 °C gave disulfide in 45% yield within 10 h without formation of undesired symmetric sulfide. The starting halide was consumed within 8 h. However, when $NaHCO_3$ was replaced by Na_2CO_3, the reaction yield increased to 87% without formation of any side product.

Given the special status of water in green chemistry, we decided to investigate this reaction in H_2O too. The reaction conditions for efficient conversion of octyl bromide to dioctyl disulfide in H_2O without formation of undesired symmetric sulfide was investigated. In one experiment, the target disulfide was obtained in 86% yield within 8 h by stirring a mixture of octyl bromide (2.0 mmol), thiourea (2.2 mmol), $NaHCO_3$ (3.0 mmol) and sodium dodecyl sulfate (SDS) (5 mol%) in H_2O (1 mL) in an oil bath at 80–90 °C. the starting halide was consumed within 6 h. Further experiments revealed that both concentration of SDS and reaction temperature play crucial roles on the reaction efficiency. Decreasing the concentration of SDS micellar solution by decreasing SDS quantity or increasing the volume of H_2O, resulted in a significant increase in the reaction time and decrease in the reaction yield. In the absence of SDS, the desired disulfide was produced in trace quantities at 80–90 °C within 24 h. Also, decreasing the reaction temperature to r.t. or 40 °C caused complete failure of the reaction. With these reaction conditions in hand, we evaluated the scope and limitation of the reaction using various alkyl halides (Table 1).

Structurally diverse halides including primary, secondary, tertiary, allylic and benzylic halides were examined. As it is evident from the results shown in Table 1, the structurally diverse organic disulfides were prepared from the corresponding primary, allylic and benzylic halides in high yields in both PEG and SDS micellar media. In general, the reactions conducted in PEG were found to be much faster than those in aqueous media. The secondary halides including cyclopentyl and cyclohexyl bromides were efficiently converted to the corresponding disulfides in PEG within 10 h whereas, they were remained intact in SDS micellar media after 24 h. Exceptionally, the reaction of *tert*-butyl bromide (entry 22) as a tertiary halide in PEG at 70 °C was not satisfying, resulted the corresponding disulfide in poor yield (less than 20%) after 24 h. The similar reaction in aqueous media did not give the desired disulfide at all. The reaction of low boiling halides including ethyl bromide (entry 7), allyl bromide (entry 8), allyl chloride (entry 9), 3-chloro-2-methylpropene (entry 10), and *iso*-propyl bromide (entry 21), were conducted at 35–40 °C. All mentioned substrates were converted to the corresponding disulfides in PEG successfully. Allyl bromide (entry 8), allyl chloride (entry 9) and 3-chloro-2-methylpropene (entry 10) were also converted into the desired disulfides in H_2O in high yields using Na_2CO_3 instead of $NaHCO_3$ but, ethyl bromide and *iso*-propyl bromide were remained intact after 24 h.

After that, we focused our study on the synthesis of symmetrical

disulfides from aryl halides. In this regard, the conversion of iodobenzene to diphenyl disulfide using thiourea, and $NaHCO_3$ in the presence of CuI and Europhtal (8020) catalyst solution was studied. The results are summarized in Table 2.

The conversion in aqueous solutions was failed and the starting halide remained unreacted under reaction conditions within 24 h (Table 2, entries 1,2). The similar reactions in DMSO and DMF at 120 °C yielded the desired product in trace quantities with the recovery of unreacted starting halide (Table 2, entries 3,4). Finally, the reaction was studied in PEG-200. The reaction proceeded efficiently to completion within 12 h to give the desired diphenyl disulfide in 91% yield (Table 2, entry 5). Notably, a similar reaction in the absence of Europhtal catalyst gave diphenyl sulfide as the sole product in 89% yield. Further experiments revealed that, the reaction proceeds more sluggishly in the presence of a lower amount of CuI or at lower temperature (Table 2, entries 6,7). Next, the conversion of other aryl halides into the corresponding disulfides under optimized reaction conditions was studied. The results are shown in Table 3.

As the results presented in Table 3 show, iodo and bromo benzenes produced the corresponding disulfides in high yields. However, under reaction conditions, 2-iodo toluene (entry 12), was remained intact after 24 h due to steric hindrances. In addition, 4-chlorobenzonitrile (entry 11) as an aryl chloride, was also recovered intact from the reaction mixture after 24 h. As expected, electron-deficient aryl halides reacted slightly faster than those having electron-donating groups.

A reasonable reaction pathway is presented in Scheme 2.

CuI undergoes oxidative addition with aryl halide followed by nucleophilic substitution of halide by thiourea to form intermediate (2) which subsequently undergoes reductive elimination to regenerate Cu(I) catalyst by releasing the *S*-arylisothiouronium salt. The intermediate *S*-alkylisothiouronium halide is also synthesized from alkyl halide and thiourea through an S_N2 displacement reaction. Basic hydrolysis of the resulting salt releases the thiol moiety that under oxidation with Co^{+3} species formed by oxidation of Co^{2+} with the atmospheric oxygen [105] gives sulfenyl radical. Next, this radical is converted to target disulfide by dimerization.

4. Conclusion

Herein, we have described an efficient process for one-pot synthesis of disulfides under environmentally benign conditions by treating the alkyl and aryl halides with thiourea in the presence of Na_2CO_3, air and Europhtal sweetening catalyst in an aqueous solution or PEG. All reagents and catalysts including thiourea, atmospheric oxygen, $NaHCO_3$, CuI and Europhtal sweetening catalyst are inexpensive and commercially available. The method is simple, scalable and high yielding and free of smelly thiols. Also, it does not require harsh basic conditions and any oxidizing reagents other than atmospheric oxygen.

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