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One-Pot Synthesis of Organic Disulfides (Disulfanes) from Alkyl Halides Using Sodium Sulfide Trihydrate and Hexachloroethane or Carbon Tetrachloride in the Poly(ethylene glycol) (PEG-200)

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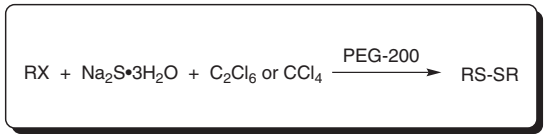

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Abstract Symmetric disulfides are produced by treating their corresponding organic halides including benzylic, allylic, primary and secondary halides with $Na_2S{\cdot}3H_2O$ and C_2Cl_6 or CCl_4 in PEG-200 at room temperature in high yields.

Key words disulfides, alkyl halides, sodium sulfide, C_2Cl_6, CCl_4, thiols

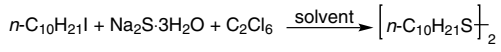
The synthesis of organic disulfides (disulfanes) is of great importance since they have many usages in industry, biology, medicine, and organic synthesis. Biologically, they have been applied in DNA-cleaving,[1] folding, stability and activity of proteins[2] and design of drug delivery systems.[3] In industry disulfide bond formation through vulcanization process, improves the tensile characteristics of polymers making them as elastic rubbers.[4] Disulfides can form a stable self-assembled monolayers on a gold surface making them essential material for construction of an electrochemical biosensor.[5] Disulfides as sulfenylating reagents have been employed in organic synthesis.[6] Diverse organosulfur compounds have been synthesized through the reaction of disulfides with epoxides,[7] Michael acceptors,[8] allenes, alkenes, alkynes,[9] carbon monoxide,[10] and thiocyanides.[11]

There are various methods for the preparation of disulfides.[12] Among them, the most efficient and popular ones involve oxidation of thiols because this process is simple, rapid and high-yielding. However, both preparation (generally from alkyl halides) and employment of thiolic precursors are very annoying due to strong and unpleasant odor of thiols. Hence, the synthesis of disulfides from alkyl halides seems synthetically more appropriate since it provides a shorter route to access disulfides and is free from thiolic smells. Conversion of alkyl halides to disulfides has been accomplished by treating an alkyl halide with elemental sulfur in the strong alkaline media or in the presence of $NaBH_4$,[13] disulfide dianion in situ generated from S/S^{2-} system,[14] and borohydride/sulfur reducing agents.[15] Rapid oxidation of a thiol that was generated in situ by reacting an alkyl halide with thiourea in the presence of a base was also applied as a strategy to form symmetrical disulfides.[16] Alkyl halides,[17] alcohols,[18] thiocyanates,[19] epoxides,[20] and aziridines[21] were also converted to disulfides by treating with benzyltriethylammonium tetrathiomolybdate efficiently. In addition, sodium *S*-alkyl thiosulfates (Bunte salts) which are produced by reacting alkyl halides with sodium thiosulfate[22] have been converted into symmetric disulfides by treating with samarium in the presence of indium(III) chloride,[23] molecular iodine,[23] thiourea, substituted thioureas, iodide ion, or thiocyanate ion.[24] However, the search for a simple, rapid and inexpensive conversion of alkyl halides into disulfides has been an interesting area of study in organic synthesis.[12a] In this paper we introduce an efficient procedure to achieve disulfides from alkyl halides, using $Na_2S{\cdot}3H_2O$, and C_2Cl_6 or CCl_4 in the poly(ethylene glycol) (PEG-200) as inexpensive and commercially available materials.

The synthesis of the symmetric sulfides by reacting two equivalents of an alkyl halide with Na_2S is a well-known reaction in organic synthesis. In this reaction, a thiolate intermediate is formed firstly which then undergoes reaction with a second molecule of alkyl halide to produce the corresponding symmetric sulfide. In the presence of an oxidizing reagent, the thiolate intermediate, partly or wholly, might be oxidized into the corresponding symmetric disulfide. To achieve disulfide without contamination with thioether, the oxidation of the thiolate intermediate should be quite facile. On the other hand, the sulfide anion as key reagent is also susceptible to oxidation and could be oxidized in the presence of many oxidizing reagents.

We now describe the development of a rapid one-pot disulfide synthesis from alkyl halides without contamination with thioether using common laboratory $Na_2S{\cdot}3H_2O$ and C_2Cl_6 or CCl_4 reagents in PEG-200. To optimize the reaction conditions, the reaction of *n*-decyl iodide, $Na_2S{\cdot}3H_2O$ and C_2Cl_6 in different solvents was studied. The results have been presented in Table 1.

Table 1 The Reaction of *n*-Decyl Iodide, $Na_2S{\cdot}3H_2O$ and C_2Cl_6 in Different Solvents[a]



Entry	Solvent	Time	Isolated yield (%)
1	H_2O	24 h	65
2	MeCN	75 min	80
3	THF	3 h	59
4	DMF	90 min	63
5	EtOH	2 h	75
6	PEG-200	90 min	94
7	CH_2Cl_2 (reflux)	24 h	No reaction

[a] Reaction conditions: *n*-$C_{10}H_{21}I$ (2 mmol), $Na_2S{\cdot}3H_2O$ (0.291 g, 2.2 mmol), C_2Cl_6 (1.5 mmol), solvent (2 mL), r.t.

The best results were obtained in poly(ethylene glycol) (PEG-200). The reaction proceeded smoothly to completion within 90 minutes at room temperature and gave the desired disulfide in 94% yield (Table 1, entry 6). The similar reactions in H_2O, MeCN, THF, DMF and EtOH gave the desired disulfide contaminated with the undesired thioether in lower yields (Table 1, entries 1–5). The reaction in refluxing CH_2Cl_2 was found to be unfavorable and the starting halide was recovered from the reaction mixture, quantitatively after 24 hours (Table 1, entry 7).

Similar results were obtained by replacing C_2Cl_6 with CCl_4. There was no significant difference in reaction times and yields when C_2Cl_6 was replaced with CCl_4. To clarify the importance of C_2Cl_6 or CCl_4 in disulfide formation, a room temperature reaction between *n*-$C_{10}H_{21}I$ (2 mmol) and $Na_2S{\cdot}3H_2O$ (0.291 g, 2.2 mmol), in PEG (2 mL) in the absence of C_2Cl_6 or CCl_4 was conducted. The non-disulfide products including didecyl thioether and *n*-decane thiol were obtained in 67% and 21% yields, respectively within 90 minutes. The similar reactions in the presence of other common laboratory oxidants (instead of C_2Cl_6 or CCl_4), including H_2O_2, CAN, oxone, sodium periodate, sodium hypochlorite, bromine, $Na_2S_2O_8$, and $KMnO_4$ were not completed and disulfide was produced in poor yields ranging from 0% to 15% after 10 hours. This could be due to the oxidation of sulfide anion by these reagents.

To prove the efficiency of the method, this procedure was then extended for the preparation of more disulfides by using the corresponding halides.[25] The results have been summarized in Table 2.

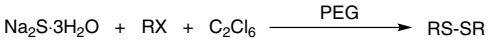
As the results show, using this method, primary, allylic, and benzylic halides were easily transformed into their corresponding disulfides in excellent yields (Table 2, entries 1–18). The scope of the reaction was extended for the preparation of more sterically hindered disulfides using cyclopentyl, cyclohexyl, and isopropyl bromides (Table 2, entries 19–21). The corresponding disulfides were produced cleanly within 2.5 hours in high yields. However, *tert*-butyl bromide was converted to the corresponding disulfide in poor yield within 10 hours (Table 2, entry 22). The protocol is applicable to large-scale operation. In this regard, the conversion of *n*-octyl bromide into its corresponding disulfide on several gram-scale was accomplished without any problem and yield loss (Table 2, entry 13).[26]

The functional group tolerance of the reaction was also investigated. 3-Chloro-1-propanol was converted into symmetric disulfide in high yield (Table 2, entry 23). Also, conversion of benzyl chloride to benzyl disulfide was performed successfully within 50 minutes in the presence of benzaldehyde, acetophenone, benzoic acid, benzonitrile, methyl benzoate and benzyl alcohol without yield-loss or any difficulty. The starting additives were recovered from the reaction mixtures almost entirely. The similar reactions in the presence of *n*-propyl amine and *p*-toluidine resulted in the desired disulfide in 70% and 76% yields, respectively within 50 minutes. Also, the corresponding benzylated amines were isolated in poor yields.

Next, a 1:1 mixture of two different alkyl halides was treated with $Na_2S{\cdot}3H_2O$ under the optimized reaction conditions. In this regard, a mixture of benzyl chloride (2 mmol) with 2-phenylethyl bromide was treated with $Na_2S{\cdot}3H_2O$ (4.4 mmol) and C_2Cl_6 (3 mmol) in PEG-200 (4 mL) at room temperature for 80 minutes. ^{13}C NMR and ^1H NMR spectrum of crude products, extracted from the reaction mixture[25] showed that a mixture of three disulfides including dibenzyl disulfide, bis(2-phenylethyl)disulfide and benzyl 2-phenylethyl disulfide were prepared in 21%, 25% and 54% yields, respectively (Table 3, entry 9). Similarly, dibenzyl disulfide, didecyl disulfide and benzyl decyl disulfide were produced in 24%, 24% and 52% yields correspondingly when a 1:1 mixture of benzyl chloride and *n*-decyl iodide was used (Table 3, entry 10).

A reasonable reaction pathway is shown in Scheme 1.

Table 2 Conversion of Organic Halides to Symmetric Disulfides Using $Na_2S·3H_2O$ and C_2Cl_6[a]



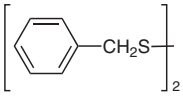
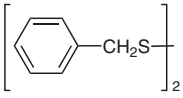
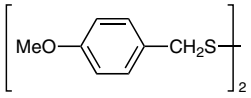
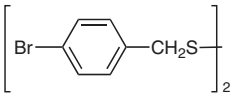
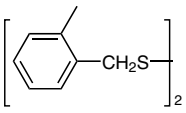
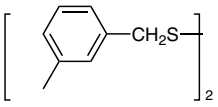
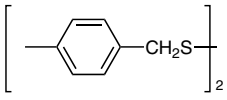
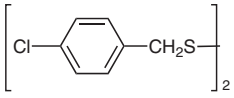
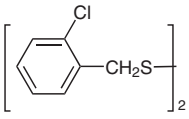
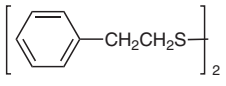
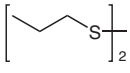
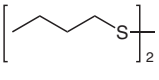
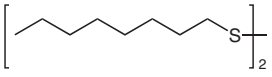
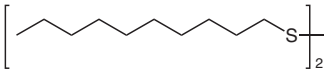
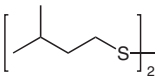
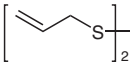
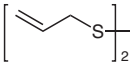
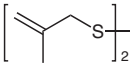
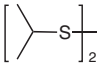
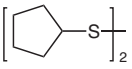
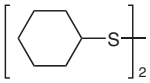
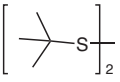
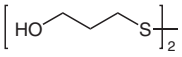
Entry	Alkyl halide	Disulfide		Time (min)[b]	Isolated yield (%)[b]
1	BnCl		(**1**)	50	91
2	BnBr		(**1**)	30	94
3	4-$MeOC_6H_4CH_2Cl$		(**2**)	40	92
4	4-$BrC_6H_4CH_2Br$		(**3**)	50	88
5	2-$MeC_6H_4CH_2Cl$		(**4**)	50	87
6	3-$MeC_6H_4CH_2Cl$		(**5**)	50	90
7	4-$MeC_6H_4CH_2Cl$		(**6**)	45	87
8	4-$ClC_6H_4CH_2CL$		(**7**)	70	88
9	2-$ClC_6H_4CH_2Cl$		(**8**)	70	91
10	$BnCH_2Br$		(**9**)	80	91
11	*n*-PrBr		(**10**)	75	86
12	*n*-BuI		(**11**)	75	89
13	*n*-$C_8H_{17}Br$		(**12**)	90	88

Table 2 (continued)

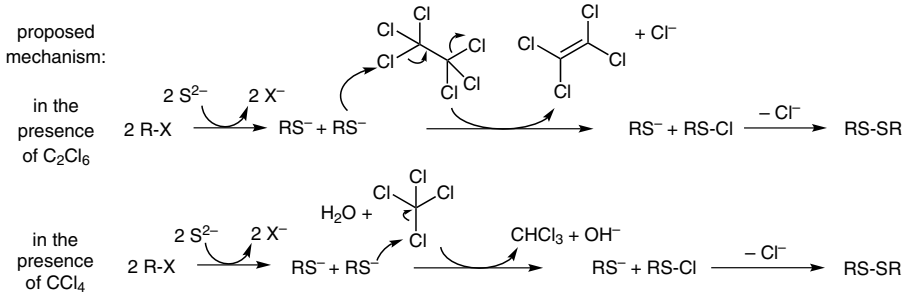
Entry	Alkyl halide	Disulfide		Time (min)[b]	Isolated yield (%)[b]
14	*n*-$C_{10}H_{21}I$		(**13**)	90	94
15	MeCH(Me)CH_2CH_2Br		(**14**)	75	91
16	CH_2=$CHCH_2Br$		(**15**)	50	93
17	CH_2=$CHCH_2Cl$		(**15**)	60	91
18	CH_2=$C(Me)CH_2Cl$		(**16**)	60	93
19	$(Me)_2CHBr$		(**17**)	150	85
20	bromocyclopentane		(**18**)	150	88
21	bromocyclohexane		(**19**)	150	90
22	$(Me)_3CBr$		(**20**)	10 h	22
23	$HOCH_2CH_2CH_2Cl$		(**21**)	120	90

[a] Reaction conditions: alkyl halide (2 mmol), $Na_2S{\cdot}3H_2O$ (0.291 g, 2.2 mmol), C_2Cl_6 (1.5 mmol), PEG-200 (2 mL), r.t.
[b] Similar results without significant differences in reaction times and yields were obtained when an alkyl halide was treated with $Na_2S{\cdot}3H_2O$ in the presence of CCl_4 instead of C_2Cl_6 under such conditions.

Table 3 Study of the Functional Group Tolerance and Synthesis of Nonsymmetric Disulfides

Entry	Reactants	Product	Yield (%)	Entry	Reactants	Product	Yield[a] (%)
1	BnCl	$(BnS)_2$	92	6	BnCl	$(BnS)_2$	92
	PhCHO	no reaction	-		BnOH	no reaction	-
2	BnCl	$(BnS)_2$	90	7	BnCl	$(BnS)_2$	70
	PhCOMe	no reaction	-		*n*-$PrNH_2$	*n*-PrNHBn	23
3	BnCl	$(BnS)_2$	89	8	BnCl	$(BnS)_2$	76
	PhCOOH	no reaction	-		4-$MeC_6H_4NH_2$	4-MeC_6H_4NHBn	19
4	BnCl	$(BnS)_2$	93	9[a]	BnCl $BnCH_2Br$	$(BnS)_2$ $(BnCH_2S)_2$ $BnSSCH_2Bn$ (**22**)	21 25 54
	PhCN	no reaction	-				
5	BnCl	$(BnS)_2$	93	10[a]	BnCl *n*-$C_{10}H_{21}I$	$(BnS)_2$ $[Me(CH_2)_9S]_2$ $BnSS(CH_2)_9Me$ (**23**)	24 24 52
	$PhCO_2Me$	no reaction	-				

[a] Yields of entries 9 and 10 were calculated from the ^1H NMR spectrum of crude products which were extracted from their reaction medium.



Scheme 1 A proposed reaction pathway

In conclusion, we have described a new procedure for the direct formation of disulfides from alkyl halides. This process has been shown to be suitable for scale-up. The preparation of structurally diverse disulfides becomes more practical using this protocol as structurally diverse organic halides are commercially available. In addition, as alkyl halides are precursors of thiols, this synthetic route provides a shorter synthetic route to disulfides of noncommercial thiols.

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(25) **General Procedure**: $Na_2S{\cdot}3H_2O$ (0.291 g, 2.2 mmol) was added to a magnetically stirred solution of an alkyl halide (2 mmol) and C_2Cl_6 or CCl_4 (1.5 mmol) in PEG-200 (2 mL) at r.t. The stirring was continued until the starting halide was completely consumed (30–150 min). Next, the reaction mixture was diluted with H_2O (1 mL) and extracted with EtOAc–hexane (1:1; 4 × 2 mL). The organic extracts were combined, concentrated and purified by chromatography on silica gel. The desired disulfides were produced in excellent yields (Table 1).

Benzyl Disulfide (1): white crystals; mp 68–70 °C [Lit.[13c] mp 69–70 °C]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.34 (m, 10 H), 3.61 (s, 4 H). ^{13}C NMR (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, 68.12; H, 5.69; S, 26.19.

Bis(2-methylbenzyl) Disulfide (4): white crystals; mp 71–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.21 (m, 8 H), 3.67 (s, 4 H), 2.38 (s, 6 H). ^{13}C NMR (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, 69.94; H, 6.50; S, 23.56.

Bis(3-methylbenzyl) Disulfide (5): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.26 (m, 2 H), 7.04–7.14 (m, 6 H), 3.60 (s, 4 H), 2.36 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 136.2, 129.1, 127.4, 127.2, 125.4, 42.3, 20.4. Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.37. Found: C, 70.16; H, 6.52; S, 23.32.

Bis(4-methylbenzyl) Disulfide (6): colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.05–7.33 (m, 8 H), 3.71 (s, 4 H), 2.21 (s, 6 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 137.6, 134.8, 129.8, 129.1, 43.1, 21.4. Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.37. Found: C, 70.05; H, 6.49; S, 23.46.

Bis(2-chlorobenzyl) disulfide (8): yellow crystals; mp70–72 °C [Lit.[27] mp 74 °C]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–730 (m, 2 H), 7.11–7.19 (m, 6 H), 3.70 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9, 133.1, 130.5, 128.8, 127.9, 125.7, 40.0. Anal. Calcd for $C_{14}H_{12}Cl_2S_2$: C, 53.34; H, 3.84; S, 20.34. Found: C, 53.21; H, 3.77; S, 20.42.

***n*-Decyl Disulfide (13)**: colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.64 (t, *J* = 7.3 Hz, 4 H), 1.59–1.71 (m, 4 H), 1.21–1.35 (m, 28 H), 0.82 (t, *J* = 6.2 Hz, 6 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 39.2, 31.8, 29.6, 29.5, 29.3, 29.2, 29.0, 28.5, 22.8, 14.2. Anal. Calcd for $C_{20}H_{42}S_2$: C, 69.29; H, 12.21; S, 18.50. Found: C, 69.16; H, 12.26; S, 18.58.

Cyclopentyl Disulfide (18): colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.39–3.45 (m, 2 H), 1.94–1.97 (m, 4 H), 1.51–1.69 (m, 12 H). ^{13}C NMR (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.

Cyclohexyl Disulfide (19): colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.64–2.73 (m, 2 H), 1.99–2.06 (m, 4 H), 1.70–1.82 (m, 4 H), 1.52–1.64 (m, 2 H), 1.17–1.31 (m, 10 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 50.1, 32.7, 26.1, 25.7. Anal. Calcd for $C_{12}H_{22}S_2$: C, 62.55; H, 9.62; S, 27.83. Found: C, 62.40; H, 9.75; S, 27.85.

Bis(3-hydroxypropyl)disulfide (21): colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (t, *J* = 6.0 Hz, 4 H), 3.02–3.14 (m, 4 H), 2.82 (br s, 2 H), 2.00–2.08 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.9, 35.2, 31.5. Anal. Calcd for $C_6H_{14}O_2S_2$: C, 39.53; H, 7.74; S, 35.17. Found: C, 39.72; H, 7.89; S, 34.98.

(26) **Typical Scale-Up Procedure for the Preparation of *n*-Octyl Disulfide**: $Na_2S{\cdot}3H_2O$ (4.365g, 33 mmol) was added to a magnetically stirred solution of *n*-octyl bromide (5.182 mL, 30 mmol) and CCl_4 (2.25 mL, 22.5 mmol) in PEG-200 (30 mL) at r.t. The starting halide was completely consumed within 90 min. Then, the mixture was diluted with H_2O (15 mL) and extracted with EtOAc–hexane (1:1; 4 × 15 mL). The upper layers were decanted, combined, and concentrated. The crude product was purified by silica gel chromatography using *n*-hexane as eluent to provide octyl disulfide in 88% yield (3.836 g) yield.

***n*-Octyl Disulfide (12)**: colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.64 (t, *J* = 7.3 Hz, 4 H), 1.53–1.68 (m, 4 H), 1.27–1.36 (m, 20 H), 0.81 (t, *J* = 6.2 Hz, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 39.2, 31.7, 29.4, 29.2, 29.1, 28.6, 22.7, 14.1. Anal. Calcd for $C_{16}H_{34}S_2$: C, 66.14; H, 11.79; S, 22.07. Found: C, 65.99; H, 11.81; S, 22.20.

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