

Rapid and efficient synthesis of symmetrical alkyl disulfides under phase transfer conditions

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Abstract—A one-pot, rapid and general method for the synthesis of symmetrical disulfides based on reaction of sulfur with sodium sulfide in the presence of didecyldimethylammonium bromide (DDAB) as a phase transfer catalyst is reported. Reaction with a variety of alkyl halides, at room temperature, afforded the disulfides in good to excellent isolated yields in a short time.

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Disulfides are important compounds possessing unique and diverse chemistry in the synthetic and biochemical areas. Large disulfide-linked aggregates are prevalent in proteins and many other bioactive molecules.¹ Industrially, disulfides find wide applications as vulcanizing agents for rubbers and elastomers, giving them excellent tensile strength. Several methods for the preparation of organic disulfides have been described.² Numerous reagents and catalysts have been applied to oxidize thiols to disulfides under controlled conditions.³ Disulfides can be easily prepared by electrochemical oxidation of the corresponding thiols in methanol/sodium methoxide solution under conditions of constant current.⁴ The catalytic couplings of thiols using Fe(III) and NaI have been reported.⁵ Disulfides were also synthesized from thiol acetate with clayfen in the absence of solvent,⁶ and via oxidative cleavage of aryl or alkyl *tert*-butyl sulfides.⁷ Recently, we reported the synthesis of disulfides through the oxidative coupling of thiols using oxygen in the presence of potassium phosphate as catalyst.⁸ Phase transfer catalysis (PTC) has been applied for the solid–liquid or liquid–liquid reactions of sulfide salts with alkyl halides. Landini and Rolla used Na₂S for the synthesis of symmetrical thioethers.⁹ This process was further studied by Sharma and Pradhan¹⁰ and by Wang and Tseng.¹¹ Aliphatic polysulfides were prepared by PTC reaction of Na₂S with dibromoalkanes.¹² Na₂S was also widely used for the reduction of nitroarenes to anilines under PTC conditions.¹³

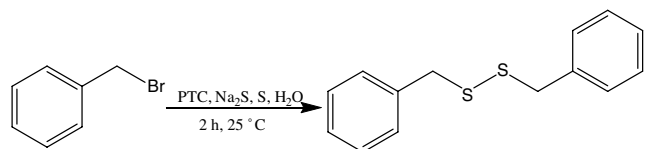
Disulfide and other polysulfide anions are easily obtained by mixing aqueous solutions of S²⁻ with sulfur. Several analytical methods were recently developed to assess the polysulfide distribution in various sulfur/sulfide mixtures.¹⁴

A mixture of Na₂S with sulfur was used by Aizenshtat in a Michael type reaction with unsaturated ketones to yield disulfides.¹⁵ Hase used Li₂S₂ for the preparation of dialkyldisulfides.¹⁶ The same reagent was later used for the synthesis of cyclic disulfides.¹⁷ The conversion of aryl/acyl halides to disulfides has also been carried out using Na₂S₂, which requires a long reaction time, and presented difficulties in isolation and required higher temperatures.^{18a,b}

Despite the plethora of methods available in the literature for the synthesis of disulfides, the search for a simple and rapid conversion of alkyl halides to disulfides is still a challenge and an interesting area of research. In continuation of our ongoing research on exploring DDAB as a phase transfer catalyst¹⁹ here we report the synthesis of disulfides from alkyl halides using DDAB as catalyst. The process affords symmetrical disulfides in good to excellent isolated yields. The reaction is fast, and is carried out at room temperature (Scheme 1).

In a generalized procedure benzyl bromide (in an organic solvent) was stirred with aqueous sodium sulfide and sulfur in the presence of various phase transfer catalysts at room temperature. We investigated the effect of different PTCs on the reaction rate and selectivity. When

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Scheme 1.

DDAB was used, the yield of the dibenzyl disulfide was high (96%) with complete conversion. The efficiency of the PTCs studied decreased in the order DDAB > TBAB > TBMAB > PEG-300. The results are summarized in Table 1.

The potential of various solvent systems such as toluene–water, methylene chloride–water, chloroform–water and ethyl acetate–water were examined in the synthesis of dibenzyl disulfide. The chloroform–water mixture was found to be the superior solvent system for the reaction.

To explore further the utility of this catalytic system, several alkyl halides were reacted under the above conditions (Table 2). All were converted into the corresponding disulfides in excellent yields. Disulfides were found to be the only products under the optimized reaction conditions.

Factors such as halide and the structure of the alkyl group profoundly influenced the course of the reaction. For example, iodides reacted quickly, whereas chlorides were rather slow. Studies were carried out to understand the influence of structural variations on the alkyl moiety. The reactivity order was found to be: benzyl halide > primary alkyl halide > secondary alkyl halide > tertiary

Table 1. Effect of various phase transfer catalysts on the synthesis of dibenzyl disulfide

Entry	PTC ^a used	Conversion ^b (%)	Yield ^c (%)
1	TBAB	95	88
2	TBMAB	91	80
3	DDAB	100	96
4	PEG-300	83	68

Reaction conditions: A mixture of sulfur powder (0.32 g, 10 mmol), sodium sulfide (1.56 g, 20 mmol), and water (5 ml) was stirred at 50 °C for 30 min. The solution was cooled to rt, PTC (4 mol %) was added, followed by substrate (20 mmol) and chloroform (5 ml) and stirring continued at 25 °C for 2 h.

^a TBAB—Tetrabutylammonium bromide; TBMAB—Tributylmethylammonium bromide; DDAB—Didecyldimethylammonium bromide; PEG—Polyethylene glycol.

^b Conversion based on gas-chromatography analysis with area minimization.

^c Isolated yields.

alkyl halide > aryl halide. While benzyl halides reacted rapidly because of the stabilization of the incipient positive charge, the lack of reactivity of tertiary halides is ascribed to steric hindrance. The reactions of aryl halides did not occur favourably under these conditions. Amongst alkyl halides, bromides were more reactive than the corresponding chlorides, which made it possible to carry out the selective synthesis of the disulfide of 1-bromo-3-chloropropane. Thus, in this study we have been able to demonstrate the utility and efficiency of DDAB as a phase transfer catalyst.

We propose a putative reaction mechanism where, in the presence of sulfur, aqueous sodium sulfide forms Na₂S₂.¹⁰ The latter reacts with the phase transfer catalyst to form the ion pair Q₂S₂, which is transferred to

Table 2. Synthesis of various disulfides using didecyldimethylammonium bromide as phase transfer catalyst^a

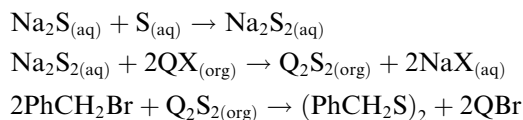
Entry	Reactant	Time (h)	Product	Conversion ^b (%)	Yield ^c /(mp/bp) (%)
1		2		100	96 (67 °C)
2		4		96	88 (65 °C)
3		2		100	91 (80 °C)
4		6		98	80 (44 °C)
5	CH ₃ (CH ₂) ₈ Br	4	CH ₃ (CH ₂) ₈ -S-S-(CH ₂) ₈ CH ₃	79	85 (oil)
6	CH ₃ -CH ₂ -I	2	CH ₃ -CH ₂ -S-S-CH ₂ -CH ₃	100	95 (152 °C)
7		9		71	62 (70 °C)
8		5		90	80 (62 °C)

^a *Reaction conditions:* A mixture of sulfur powder (0.32 g, 10 mmol), sodium sulfide (1.56 g, 20 mmol), and water (5 ml) was stirred at 50 °C for 30 min. The solution was cooled to rt, DDAB (4 mol %) was added, followed by substrate (20 mmol) and chloroform (5 ml) and stirring continued at 25 °C.

^b Conversion based on gas-chromatography analysis with area minimization.

^c Isolated yields.

the organic phase to react with the substrate to yield the dialkyl disulfide and the catalyst as follows:



Since it is known that the nature of the polysulfide anion in water (S_x^{2-} where $x = 2, 3, 4, 5$) can be determined by controlling the sulfide/sulfur ratio,²⁰ we believe that tri-, tetra- and higher dialkyl polysulfides can be synthesized using the method described above.

In conclusion, a simple, efficient and practical method has been developed for the synthesis of symmetrical alkyl disulfides using DDAB as a phase transfer catalyst.

General procedure: A mixture of sulfur powder (0.32 g, 10 mmol), sodium sulfide (1.56 g, 20 mmol) and water (5 ml) was stirred vigorously for 30 min at 50 °C. After dissolution, the reaction mixture was cooled to room temperature and DDAB (4 mol %) was added. A mixture of substrate (20 mmol) and chloroform (5 ml) was added and the mixture was stirred for an appropriate period at 25 °C. The progress of the reaction was monitored by GC. After completion of the reaction, the product was extracted with two consecutive portions of diethyl ether; the combined organic layers were washed well with water and dried over sodium sulfate. The organic layer was concentrated under reduced pressure to afford a crystalline (or liquid) dialkyl disulfide.

Pure solid products were obtained by purification on a short silica gel column using petroleum ether as the eluent and recrystallization from ethanol. All the products had satisfactory ¹H NMR, IR and elemental analysis data and were compared with authentic samples.

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