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A simple, economical, and catalyst-free oxidation of thiols to disulfides

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A simple, rapid, and highly efficient method for the preparation of symmetrical aliphatic, aromatic, and heteroaromatic disulfides is reported. Addition of NBS to an alkyl- or arylthiol under catalyst-free conditions in dichloromethane solution produces the corresponding disulfides in nearly quantitative yields.

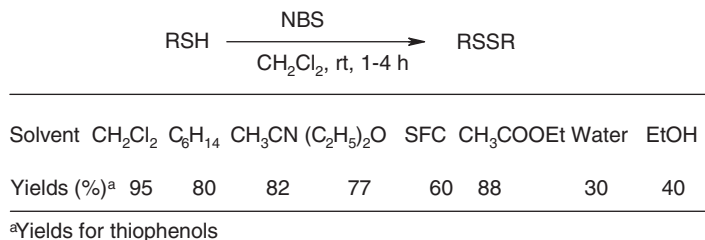
Keywords: disulfides; thiols; *N*-bromosuccinimide; oxidation; catalyst-free

Disulfides play significant roles in biological and chemical processes and serve as versatile reagents in organic synthesis (1). Among several methods of preparing disulfides, the most efficient and popular involve oxidation of thiols because a large number of thiols are commercially available or can be easily synthesized. Reagents such as cerium(IV) salts (2), permanganates (3), transition metal oxides (4), air in combination with transition metal catalysts (5), sodium perborate (6), ferric chloride (7), sodium chlorite (8), nitric oxide (9), hydrogen peroxide (10) and halogens (11), have been utilized for oxidation of thiols to disulfides. However, many of these methods involve strong acidic or oxidizing conditions, and expensive and hazardous reagents. Therefore, development of inexpensive reagents with greater efficiency and more convenient procedures with better yields are of great interest. A popular, less hazardous, and inexpensive reagent that has been used for mild oxidation is *N*-bromosuccinimide (NBS) (12). The major advantage of using NBS as an oxidizing agent is that the succinimide byproduct can be easily recovered and reconverted to NBS and can be reused. Furthermore, to the best of our knowledge there is no report on catalyst-free oxidation of thiols with NBS in the literature.

As part of our research on oxidation of organic compounds, especially thiols with different oxidizing agents (13–15), we developed a much more simple, efficient and practical procedure with improved yields and short times, by using NBS as a commercially available and inexpensive reagent for the synthesis of disulfides (Scheme 1).

The reactions were carried out in the simplest manner, by mixing the thiols and the NBS in dichloromethane as a solvent at room temperature. The best result was obtained by using 0.5 equiv of NBS. Oxidation of thiols with NBS proceeded smoothly at room temperature to

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Scheme 1.

afford the corresponding disulfides in high yields in a short reaction time. The reactions were also carried out in other solvents such as petroleum ether, diethyl ether, and ethyl acetate. All of these solvents give the corresponding disulfides in high yields; however, in the case of protic solvents, such as methanol, further oxidation of thiol to benzenesulfonic acid has been observed. The results for the oxidation of thiols with NBS are summarized in Table 1, and clearly indicate the scope of the reaction with respect to various thiols. To establish the generality, NBS was treated with various thiols and in all cases, good yields were obtained with aromatic and aliphatic thiols in dichloromethane at room temperature (21).

The comparison of the present method with respect to the amount of thiols, reaction time and yields with those of the literature reports dealing with oxidation of thiol to disulfides, shows that our method is superior to many of the reported procedures.

To show the advantages and potential drawbacks of this reagent over some other oxidations, we have compared our results with thiophenol with those reported in the literature in Table 2.

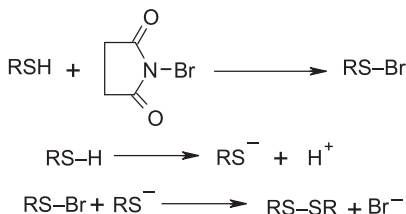
Although no detailed mechanistic studies have been carried out, we believe the reactions proceed through halogen transfer from NBS to thiols to yield sulfenyl bromide, which reacts with a thiolate anion to yield disulfides and hydrobromic acid. This mechanism is supported by the observation that in the workup step, water becomes acidic (Scheme 2).

Table 1. Oxidation of thiols to disulfides in the presence of NBS.

Entry	R	Time (min)	Yield (%)
1	C ₆ H ₅	5	95
2	C ₆ H ₅ CH ₂	5	93
3	4-CH ₃ C ₆ H ₄	5	96
4	4-BrC ₆ H ₄	3	97
5	2-naphthyl	5	92
6	1-butyl	5	95
7	2-butyl	5	93
8	1-octyl	10	90
9	1-ethyl	5	80
10	2-methyl-2-ethyl	12	85

Table 2. Comparison of NBS with some of the other reagents for oxidation of thiols.

Substance	Conditions	Time (min)/Yield (%)	Reagent	Reference
PhSH	CH ₂ Cl ₂ /RT	5/95	NBS	–
PhSH	CH ₃ CN/RT	8/93	2,6-DCPCC	(16)
PhSH	CH ₃ CN/RT	120/99	Bu ₃ SnOMe/FeCl ₃	(17)
PhSH	CH ₂ Cl ₂ /20 °C	114/94	PCC	(18)
PhSH	Solid state	10/79	(NH ₄) ₂ S ₂ O ₈	(19)
PhSH	CH ₃ CN/RT	270/93	Carols acid/SiO ₂	(20)



Scheme 2. Proposed mechanism for the formation of a disulfide from a thiol.

In summary, we have demonstrated an economical and practical method for the synthesis of a wide range of disulfides under mild conditions. In the light of its operational simplicity, simple purification procedure, high yields, room temperature conditions and short reaction time without a catalyst, the method is superior to any existing traditional method.

Acknowledgement

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- (21) *General procedure for the preparation of disulfides*: To the stirred solution of thiols (1 mmol) in dichloromethane (5 ml), NBS (0.5 mmol) was added. The resulting mixture was stirred at room temperature by the time indicated in Table 1. The progress of the reaction was monitored by TLC. After the completion of the reaction, CH_2Cl_2 (10 ml) was added and the mixture was washed successively with water (2×20 mL). The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave almost pure product. Further purification was achieved by column chromatography on silica gel or recrystallization from EtOAc–hexane to give pure product in good to excellent yield (Table 1). The products were characterized by comparison of spectral data with those of authentic samples.