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A one-pot, efficient, and odorless synthesis of symmetrical disulfides using organic halides and thiourea in the presence of manganese dioxide and wet polyethylene glycol (PEG-200)

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ABSTRACT

Primary, secondary, tertiary, allylic, and benzylic halides are converted efficiently into symmetric disulfides in high yields using thiourea as the sulfur atom source. The reactions are odorless and are performed at 30–35 °C in wet PEG-200 using MnO_2 as an oxidant.

Sulfur–sulfur bonds as found in peptides and many other bioactive molecules play an important role in their biological activity.[1] In industry, rubbers and elastomers are vulcanized using this linkage to improve their tensile strength.[2] Moreover, it has been found that several molecules containing a disulfide linkage have potential applications in optical data processing and communication.[3]

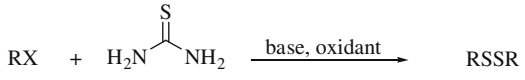
In organic synthesis, especially in recent years, a great deal of attention has been paid to the scope and application of disulfides. Sulfur–sulfur-containing compounds can serve as important auxiliary functions in the synthesis of diverse organic compounds such as 3-(arylthio)indoles,[4] thia-Michael adducts,[5] and β-hydroxy thioethers via ring opening of epoxides.[6] Moreover, insertion of allenes,[7] alkenes, alkynes, carbon monoxide, and thiocyanides into sulfur–sulfur bonds is a useful synthetic method for the preparation of organo-sulfur compounds via C–S bond formation.[8] The oxidative coupling of thiols to their corresponding disulfides is the most common method for disulfide formation.[9] Although these methods are very effective, they have environmental and safety problems. The main drawbacks are the use of highly volatile and foul-smelling thiols in organic solvents which are expensive, toxic, flammable, and not recyclable. In addition to thiol oxidation methods, there are several other methods for the preparation of disulfides from nonthiolic precursors, of which, conversion of alkyl halides into disulfides is valuable.[10] A literature survey revealed only a few reports on the one-pot conversion of alkyl halides into disulfides. In this regard, alkyl halides were converted into their corresponding symmetric disulfides using alkali metal disulfides,[2,11] and sulfated borohydride exchange resin.[12] *S*-Alkylisothiouronium salts were also converted into disulfides using strongly basic hydrogen peroxide solution.[13]

Polyethylene glycols (PEGs) are cheap, have negligible vapour pressure, are thermally stable, recoverable, nontoxic, and eco-friendly, and thus are useful media for chemical reactions.[14]

In this study, we describe a new method for the one-pot preparation of disulfides from their corresponding alkyl halides which is free from foul-smelling thiols. Wet polyethylene glycol (PEG-200), thiourea, MnO_2, and Na_2CO_3 are used.

Basic hydrolysis of *S*-alkylisothiouronium salts which are generated from the reaction of alkyl halides and thiourea is one of the most common methods for thiol synthesis. Thiol oxidation is the general accepted route for disulfide preparation. Therefore, we studied the possibility of the direct generation of disulfides from their corresponding organic halides using thiourea, a base and a suitable oxidizing agent (Scheme 1).

To optimize the reaction conditions, we studied the reaction of benzyl chloride (2 mmol) with thiourea (3 mmol) in the presence of Na_2CO_3 (3 mmol) and different oxidants including H_2O_2, oxone, sodium and potassium periodate, sodium hypochlorite, iodine, bromine, $Na_2S_2O_8$, $KMnO_4$, $BaMnO_4$,[15] and MnO_2 in wet polyethylene glycol (2 mL of PEG-200 and 0.15 mL of H_2O) at 30–35 °C. We found that oxidizing agents such as H_2O_2, Oxone, sodium and potassium periodate, sodium hypochlorite, iodine, $Na_2S_2O_8$, and bromine were not suitable for the reaction. However, in the presence of MnO_2 or $BaMnO_4$ (2 mmol) the corresponding disulfide was produced cleanly in 80–84% isolated yield after four hours. Reaction with $KMnO_4$ (2 mmol) was not clean and only 60% of the disulfide was isolated after seven hours. This protocol was then



Scheme 1. Formation of disulfides from the reaction of organic halides with thiourea in the presence of an oxidant.

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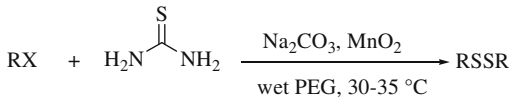
Table 1
One-pot transformation of alkyl halides into their corresponding symmetric disulfides



Entry	Alkyl halide	Product[a]	Time (h)	Isolated yield (%)
1	*n*-Decyl iodide	$(n\text{-}C_{10}H_{21}S\text{–})_2$	12	85
2	*n*-Octyl iodide	$(n\text{-}C_8H_{17}S\text{–})_2$	10	86
3	*n*-Octyl bromide	$(n\text{-}C_8H_{17}S\text{–})_2$	12	86[b]
4	*n*-Butyl iodide	$(n\text{-}C_4H_9S\text{–})_2$	3.5	85
5	*n*-Butyl bromide	$(n\text{-}C_4H_9S\text{–})_2$	5	87
6	*n*-Propyl iodide	$(n\text{-}C_3H_7S\text{–})_2$	3	86
7	Ethyl bromide	$(C_2H_5S\text{–})_2$	3.5	80
8	Allyl bromide	$(CH_2{=}CHCH_2S\text{–})_2$	3	87
9	Allyl chloride	$(CH_2{=}CHCH_2S\text{–})_2$	5	85
10	3-Chloro-2-methyl-propene	$(CH_2{=}C(CH_3)CH_2S\text{–})_2$	5	88
11	Benzyl bromide	$(PhCH_2S\text{–})_2$	2.5	86
12	Benzyl chloride	$(PhCH_2S\text{–})_2$	4	86
13	4-Methylbenzyl chloride	$(4\text{-}CH_3C_6H_4CH_2S\text{–})_2$	3	84
14	4-Bromobenzyl chloride	$(4\text{-}BrC_6H_4CH_2S\text{–})_2$	6	83
15	(2-Bromoethyl)benzene	$(PhCH_2CH_2S\text{–})_2$	9	87
16	Cyclohexyl bromide	(cyclohexyl-S–)$_2$	36	82
17	Cyclopentyl bromide	(cyclopentyl-S–)$_2$	30	85
18	*iso*-Propyl bromide	$[(CH_3)_2CHS\text{–}]_2$	36	77
19	*tert*-Butyl bromide	$[(CH_3)_3CS\text{–}]_2$	72	65

[a] All products were identified from their ^{1}H NMR and ^{13}C NMR spectra and elemental analyses.
[b] The reaction was applied for the large-scale operation using 40 mmol of *n*-octyl bromide.

applied for the preparation of different symmetric disulfides using MnO_2.[16] The results are shown in Table 1.

Using this method, primary, allylic, and benzylic halides were easily transformed into their corresponding disulfides in good to excellent yields (Table 1, entries 1–15). We also extended our studies for the preparation of more sterically hindered disulfides. Cyclopentyl, cyclohexyl, *iso*-propyl, and *tert*-butyl disulfides were prepared from their corresponding organic bromides in high yields within 30–72 h (Table 1, entries 16–19).

This protocol was easily applicable to scale-up. For example, the direct conversion of *n*-octyl bromide into its corresponding symmetric disulfide on several gram-scale was carried out successfully (Table 1, entry 3).[17]

In conclusion, we have described a novel one-pot odorless process for the formation of disulfides from alkyl halides. This method is conducted under mild conditions and is suitable for scale-up. As structurally diverse organic halides are readily available and their synthesis is much easier than the corresponding thiols, the preparation of structurally diverse disulfides becomes more practical using this protocol.

Acknowledgment

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16. *General procedure*: To a solution of thiourea (3 mmol) in PEG 200 (2 mL) were added an alkyl halide (2 mmol), H_2O (0.15 mL), MnO_2 (2 mmol), and Na_2CO_3 (3 mmol). The mixture was stirred magnetically at 30–35 °C. The progress of the reaction was monitored by TLC or GC until the alkyl halide was consumed. After completion of the reaction, the mixture was extracted with low-boiling petroleum ether (5 × 2 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 chromatography using low-boiling petroleum ether as an eluent to provide the desired product in 65–88% yields.
17. Typical scale-up procedure for the conversion of *n*-octyl bromide into its corresponding symmetrical disulfide: To a solution of thiourea (60 mmol, 4.57 g), *n*-octyl bromide (40 mmol, 7.72 g), H_2O (3 mL) in PEG-200 (60 mL), MnO_2 (40 mmol, 3.48 g), and Na_2CO_3 (60 mmol, 6.36 g) were added. The mixture was stirred at 30–35 °C. The progress of the reaction was monitored by GC until the alkyl bromide was consumed (12 h). The mixture was extracted with low-boiling petroleum ether (5 × 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to yield the crude product, which was further purified by silica gel chromatography using low-boiling petroleum ether as an eluent to provide the desired product in 86% (5.00 g) yield. *1,2-Dioctyl disulfide*: Colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.61 (t, J = 7.3 Hz, 4H), 1.66–1.54 (m, 4H), 1.30–1.21 (m, 20H), 0.84–0.79 (m, 6H); ^{13}C NMR (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, 66.21; H, 11.71; S, 22.08.