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Reduction of sulfur with borohydride exchange resin in methanol: application to rapid and selective synthesis of disulfides

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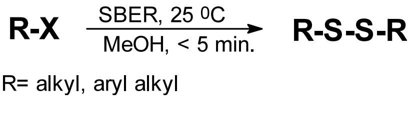
Abstract—A convenient and rapid method for the synthesis of symmetrical disulfides from alkyl or aryl alkyl halides using sulfurated borohydride exchange resin (SBER) under anhydrous conditions is described. Selective transfer of sulfur to an alkyl group rather than an aryl group is achieved using this methodology. © 2001 Elsevier Science Ltd. All rights reserved.

The disulfide moiety occurs ubiquitously in proteins and is also found in a variety of natural products and pharmacologically active compounds.[1] In addition, cyclic and acyclic disulfides are useful intermediates in the synthesis[2] and preparation of adsorbed monolayers.[3] Acyclic[4] and cyclic disulfides are typically prepared by the oxidative dimerization of α-ω-dithiols (e.g. I_2, NEt_3;[5] Br_2;[6] $K_3Fe(CN)_6$;[7] CCl_4, NEt_3;[8] H_2O_2/KI/AcOH;[9] $Pb(OAc)_4$, S;[10] KO_2;[11a] Caro's acid supported on silica gel[11b]) and may also be prepared by reacting α,ω-dihalogenated compounds with Na_2S/S_8[12] or from thiocyanates with base (eg. NaOH or NH_3).[13] More recently, reaction of α,ω-bisthiocyanates with samarium diiodide[14] or tetrathiomolybdate[15] or tetrabutylammonium fluoride[16] have been employed in the synthesis of cyclic disulfides. Thus, most of the disulfides are prepared from the corresponding thiols/dithiols by conventional oxidation.[17] The major problem associated with this strategy is that, in general, it leads to the formation of dimer, trimer and polymers to an appreciable amount thereby reducing the yield of the desired product considerably.[17a] The synthesis of disulfides via bisthiocyanates starting from dihalides[18] is a two step process and thus the overall yield of the product is lowered.

In this communication, we describe our results for the first time on a facile sulfur transfer reaction using sulfurated borohydride exchange resin (SBER) in methanol for a rapid and selective synthesis of a variety of acyclic and cyclic disulfides from alkyl or aryl alkyl halides in high yield (Scheme 1).

When borohydride exchange resin (BER),[19] sulfur and a halide or dihalide in methanol is stirred, a spontaneous reaction took place (<5 min) giving the corresponding disulfide in good to excellent yield. The results are presented in the Table 1. The reaction is found to be general as primary, secondary, tertiary, benzylic, allylic halides as well as dihalides underwent smooth reaction giving the corresponding acyclic and cyclic disulfides. It is important to note that the reaction appears to be specific only for alkyl halides as aryl halides failed to undergo the reaction (entries 6–10). Therefore, it is a method of choice for the synthesis of disulfides from alkyl halides in the presence of aryl halides. In this connection it should be mentioned that a recent report[15] for the synthesis of disulfides employing tetrathiomolybdate does not discriminate between aryl halides and aryl alkyl halides. Another important feature of this method is that the reaction is very rapid giving pure products in high yield compared with reported methods.[15] It must be mentioned that several other functional groups present in the molecule such as F (entry 6), Cl (entries 7, 9), Br (entry 10), CN (entries 11, 20), NO_2 (entries 12, 21), OMe (entries 8, 18), methylenedioxy (entry 9), $NHCOCH_3$ (entry 19), acetal (entry 22), allylic C=C (entries 1, 23) ester (entries 5, 15) and polyethers (entries 16, 17) remain intact under these reaction conditions.



Scheme 1.

Keywords: alkyl halide; disulfide; SBER; selectivity.

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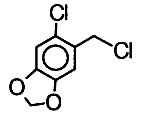
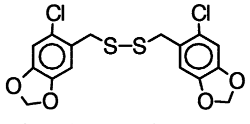
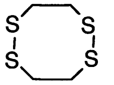
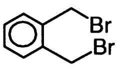
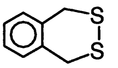
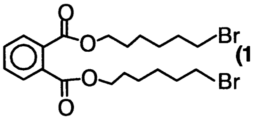
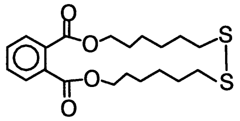
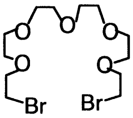
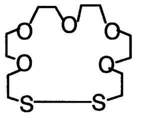
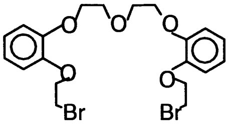
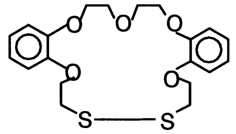
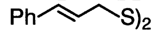
Table 1. Synthesis of disulfides using SBER at 25°C

Entry	Halide		Product		Yield[a,b] (%)
1	Allyl bromide	**(1a)**	Diallyl disulfide	**(2a)**	85
2	Dodecyl bromide	**(1b)**	Didodecyl disulfide	**(2b)**	88
3	Cyclohexyl bromide	**(1c)**	Dicyclohexyl disulfide	**(2c)**	85
4	t- Butyl bromide	**(1d)**	Di- t- butyl disulfide	**(2d)**	75
5	Br CH_2COOEt	**(1e)**	$(SCH_2COOEt)_2$	**(2e)**	72
6	4-F $C_6H_4CH_2Br$	**(1f)**	(4-F $C_6H_4CH_2S)_2$	**(2f)**	91
7	4-$ClC_6H_4CH_2Br$	**(1g)**	(4-Cl $C_6H_4CH_2S)_2$	**(2g)**	89
8	4-$MeOC_6H_4CH_2Cl$	**(1h)**	(4-$MeOC_6H_4CH_2S)_2$	**(2h)**	88
9		**(1i)**		**(2i)**	75
10	4-Br $C_6H_4CH_2Br$	**(1j)**	(4-Br $C_6H_4CH_2S)_2$	**(2j)**	83
11	4-CN $C_6H_4CH_2Br$	**(1k)**	(4-CN $C_6H_4CH_2S)_2$	**(2k)**	85
12	4-NO_2 $C_6H_4CH_2Br$	**(1l)**	(4-NO_2 $C_6H_4CH_2S)_2$	**(2l)**	80
13	Br—CH_2—CH_2—Br	**(1m)**		**(2m)**	65
14		**(1n)**		**(2n)**	91
15		**(1o)**		**(2o)**	72
16		**(1p)**		**(2p)**	82
17		**(1q)**		**(2q)**	79
18	$Br(CH_2)_6OMe$	**(1r)**	$S[(CH_2)_6OMe]_2$	**(2r)**	83
19	$Br(CH_2)_5NHCOCH_3$	**(1s)**	$S[(CH_2)_5NHCOCH_3]_2$	**(2s)**	81
20	$Br(CH_2)_6CN$	**(1t)**	$S[(CH_2)_6CN]_2$	**(2t)**	89
21	$Br(CH_2)_6NO_2$	**(1u)**	$S[(CH_2)_6NO_2]_2$	**(2u)**	84
22	$BrCH_2(OEt)_2$	**(1v)**	$S[CH_2(OEt)_2]_2$	**(2v)**	80
23		**(1w)**		**(2w)**	88

a. Yields of pure isolated products b. Products are characterized by their physical constants and spectral analysis

In order to explore the generality and scope of SBER for the synthesis of disulfides, the procedure has been extended to the synthesis of an important class of compounds: macrocyclic disulfides (redox switched crown ethers)[17a,b,20] in high yield (entries 15 and 17).

In summary, we have demonstrated that SBER serves as an efficient reagent for the synthesis of acyclic and cyclic disulfides from the corresponding alkyl or aryl alkyl halides under mild and essentially neutral conditions. The effectiveness of this protocol is manifested in its selectivity towards alkyl halides whereas aryl halides and other reducible groups are found to be unreactive under these reaction conditions. The obvious advantages of heterogeneous reagent in terms of simple operation with the ease of work-up and recyclability of the resin are noteworthy. We believe that this method will present a better and more practical alternative to the existing methodologies and should find widespread applications in organic synthesis.

Typical procedure: A mixture of borohydride exchange resin (5 gm, 5 mmol) and sulfur powder (5 mmol) in methanol (10 ml) is stirred at room temperature for 10 min. Then 4-chlorobenzyl chloride (5 mmol) is added and stirred for 5 min. After completion of the reaction (TLC), the resin was filtered off and solvent was removed under reduced pressure to afford the product, **2g** in almost pure form which was further purified by column chromatography on silica gel (hexane:ethyl acetate, 9:1).

Spectroscopic data of some selected compounds

Compound **2j**: mp = 149–151°C; IR (KBr, cm^{-1}): 600, 676, 876, 1011, 1069, 1095, 1178, 1199, 1264, 1305, 1401, 1590, 1699, 1898, 2854, 2920, 2963, 3039; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.5$ (s, 4H, SCH_2); 7.25 (d, 4H, $J = 8.7$ Hz, Ar-H); 8.12 (d, 4H, $J = 8.7$ Hz, Ar-H). Mass: m/z (%) = 404 (M$^+$, 8); 169 (100). Anal. calcd for: $C_{14}H_{12}Br_2S_2$ (404): C, 41.58; H, 2.97; Br, 39.60; S, 15.84. Found: C, 41.63; H, 3.03; Br, 39.48; S, 15.93.

Compound **2l**: mp = 83°C; IR (KBr, cm^{-1}): 620, 721, 769, 832, 865, 935, 984, 1036, 1117, 1176, 1233, 1253, 1360, 1413, 1479, 1503, 1619, 2892, 3010; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.6$ (s, 4H, SCH_2); 7.29 (d, 4H, $J = 7.5$ Hz, Ar-H); 8.17 (d, 4H, $J = 7.5$ Hz, Ar-H). Mass: m/z (%) = 336 (M$^+$, 5); 136 (100). Anal. calcd for: $C_{14}H_{12}N_2O_4S_2$ (336.3944): C, 49.99; H, 3.95; N, 8.33; S, 19.07. Found: C, 49.91; H, 3.65; N, 8.28; S, 19.14.

Compound **2o**: Viscous liquid; IR (neat, cm^{-1}): 760, 1120, 1220, 1450, 1500, 1602, 1740, 2822, 3017; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.1–1.8$ (m, 16H); 2.4–2.8 (t, $J = 2.4$ Hz, 4H); 4.2 (t, 4H, $J = 3.1$ Hz, CH_2O); 7.50–7.80 (M, 4H, Ar-H). Mass: m/z (%) = 396.57 (M+, 14); 149 (100). Anal. calcd for: $C_{20}H_{28}O_4S_2$ (396.5728): C, 60.57; H, 7.12; S, 16.17. Found: C, 60.64; H, 7.05; S, 16.23.

Compound **2q**: mp = 127–128°C; IR (KBr, cm^{-1}): 753, 1050, 1120, 1222, 1250, 1460, 1505, 1597, 2830, 3020; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.22$ (t, 4H, $J = 4.5$ Hz, CH_2S); 3.85–4.30 (m, 12H, CH_2O); 6.92 (s, 8H, Ar-H). Mass: m/z (%) = 408.54 (M+, 100); 136 (73). Anal. calcd for: $C_{20}H_{24}O_5S_2$ (408.5411): C, 58.80; H, 5.52; S, 16.70. Found: C, 58.82; H, 5.84; S, 16.61.

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