Monatsh Chem 139, 1453–1456 (2008)
DOI 10.1007/s00706-008-0950-0
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

The rapid and efficient synthesis of disulfides from alkyl and acyl halides

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Received 8 August 2007; Accepted 28 January 2008; Published online 9 June 2008

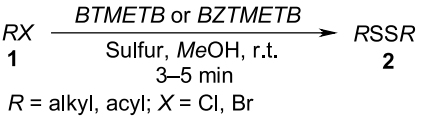
Abstract Various symmetrical dialkyl and diacyl disulfides are prepared easily in high yields from the corresponding alkyl and acyl halides under mild and nonaqueous conditions using *N*,*N*′-dibutyl-*N*,*N*,*N*′,*N*′-tetramethyl-ethylenediammonium tetrahydroborate (*BTMETB*) or *N*,*N*′-dibenzyl-*N*,*N*,*N*′,*N*′-tetramethylethylenediammonium tetrahydroborate (*BZTMETB*) and elemental sulfur. The quarternary diammonium borohydrides were easily prepared by treatment of the corresponding quarternary diammonium chloride or bromide with alkaline solution of sodium borohydride at room temperature.

Keywords Sulfur; Quarternary diammonium borohydride; Disulfide; Acyl halide; Alkyl halide.

Introduction

Disulfides play significant roles in biological and chemical processes and serve as versatile reagents in organic synthesis [1]. In addition, disulfides are an important class of synthetic intermediates in a variety of chemical transformations. Much attention has been given to the synthesis of disulfides from the oxidation of thiols and thiocarboxylate ions to alkyl and acyl disulfides under controlled conditions [2–17]. The most commonly used methods for direct conversion of alkyl and acyl halides to disulfides have been using Na_2S_2, Na_2S/S, or H_2S_2 [18]. In recent years, new methods have been developed for the introduction of sulfur into organic molecules using benzyltriethylammonium tetracosathioheptamolybdate $[(C_6H_5CH_2N(Et)_3)_6Mo_7S_{24}]$ [19], sodium hydroxide under phase transfer conditions (PTC) [20], samarium diiodide [21], hydroxide form of Amberlist [22], and borohydride exchange resin [23]. However, these methods suffer from severe disadvantages, such as low yields, long reaction times, use of aqueous medium, the need for reactions to be carried out under PTC conditions, formation of by products, toxic solvents, and hydrolysis of some acyl chlorides under reaction conditions. Therefore, the introduction of a clean, mild, and efficient method to synthesize alkyl and acyl disulfides is still in demand.

In this communication, we wish to report an improved, efficient, rapid, easy, and high yield synthesis of dialkyl and diacyl disulfides, under mild and nonaqueous conditions using sulfur and *N*,*N*′-dibutyl-*N*,*N*,*N*′,*N*′-tetramethylethylenediammonium tetrahydroborate (*BTMETB*) or *N*,*N*′-dibenzyl-*N*,*N*,*N*′,*N*′-tetramethylethylenediammonium tetrahydroborate (*BZTMETB*) (Scheme 1).



Scheme 1

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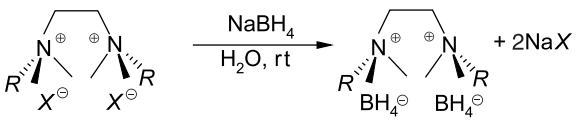
Results and discussion

BTMETB and *BZTMETB* are white powders and stable compounds which are prepared quantitatively by treatment of aqueous solutions of the corresponding quarternary diammonium chloride or bromide with alkaline sodium borohydride solution at room temperature (Scheme 2).

When *BTMETB* or *BZTMETB*, sulfur, and an alkyl or acyl halide in methanol was stirred, a spontaneous reaction took place giving the corresponding disulfide in good to excellent yield at room temperature.

The reaction is found to be general as primary, secondary, tertiary, benzylic, and allylic halides as well as acyl chlorides underwent the reaction giving the corresponding disulfides. The results are shown in Table 1. It is important to note that the reaction appears to be specific only for alkyl halides as aryl halides failed to undergo the reaction. Therefore, it is a method of choice for the synthesis of disulfides from alkyl halides in the presence of aryl halides. Another important feature of this method is that the reaction is very rapid giving pure products in high yield. It must be mentioned that several other functional groups present in the molecule such as Cl (entries 3–5, 15–17), Br (entry 6), NO_2 (entry 7), *Me*O (entry 8), CO (entries 9, 14–18), and C=C bond (entry 12) remain intact under the reaction conditions.



Scheme 2

It is interesting to mention that conversion of alkyl and acid halides to their corresponding disulfides with $NaBH_4$ and $NaBH_4$ in the ammonium phase transfer catalyst proceeded very exothermally and give lower yield of the corresponding disulfides. However, lowering the temperature to −15°C did not improve the yield of the reactions.

In conclusion, we demonstrated that sulfur and quarternary diammonium borohydrides serve as efficient reagents for the synthesis of alkyl and acyl disulfides from the corresponding alkyl and acyl halides under mild conditions. The effectiveness of this protocol is manifested in its selectivity towards alkyl halides whereas aryl halides and other reduc-

Table 1 Synthesis of disulfides **2a**–**2p** using *BTMETB* and *BZTMETB*[a]

RX		Product[b]		*BTMETB*		*BZTMETB*	
				Time/min	Yield[c]/%	Time/min	Yield[c]/%
Ph–CH_2Cl	(**1a**)	(*Ph*–$CH_2S)_2$	(**2a**)	5	87	5	85
Ph–CH_2Br	(**1′a**)	(*Ph*–$CH_2S)_2$	(**2a**)	5	90	5	90
3-Cl–$C_6H_4CH_2Cl$	(**1b**)	(3-Cl–$C_6H_4CH_2S)_2$	(**2b**)	5	81	5	82
3-Cl–$C_6H_4CH_2Br$	(**1′b**)	(3-Cl–$C_6H_4CH_2S)_2$	(**2b**)	5	83	5	86
4-Cl–$C_6H_4CH_2Cl$	(**1c**)	(4-Cl–$C_6H_4CH_2S)_2$	(**2c**)	5	82	5	80
4-Br–$C_6H_4CH_2Br$	(**1d**)	(4-Br–$C_6H_4CH_2S)_2$	(**2d**)	5	90	5	86
4-O_2N–$C_6H_4CH_2Cl$	(**1e**)	(4-O_2N–$C_6H_4CH_2S)_2$	(**2e**)	5	82	5	84
4-*Me*O–$C_6H_4CH_2Cl$	(**1f**)	(4-*Me*O–$C_6H_4CH_2S)_2$	(**2f**)	5	86	5	86
Ph–$COCH_2Br$	(**1g**)	(*Ph*–$COCH_2S)_2$	(**2g**)	5	88	5	90
1-$C_{10}H_7CH_2Cl$	(**1h**)	(1-$C_{10}H_7CH_2S)_2$	(**2h**)	5	77	5	79
c–$C_6H_{11}Br$	(**1i**)	(*c*–$C_6H_{11}S)_2$	(**2i**)	5	75	5	78
CH_2=$CHCH_2Br$	(**1j**)	(CH_2=$CHCH_2S)_2$	(**2j**)	5	78	5	78
$(CH_3)_3CBr$	(**1k**)	$[(CH_3)_3CS]_2$	(**2k**)	5	75	5	75
Ph–COCl	(**1l**)	(*Ph*–$COS)_2$	(**2l**)	3	90	3	90
4-Cl–C_6H_4COCl	(**1m**)	(4-Cl–$C_6H_4COS)_2$	(**2m**)	3	83	3	80
3-Cl–C_6H_4COCl	(**1n**)	(3-Cl–$C_6H_4COS)_2$	(**2n**)	3	78	3	81
2-Cl–C_6H_4COCl	(**1o**)	(2-Cl–$C_6H_4COS)_2$	(**2o**)	3	76	3	75
4-*Me*O–C_6H_4COCl	(**1p**)	(4-*Me*O–$C_6H_4COS)_2$	(**2p**)	3	81	3	80

[a] All reactions were carried out at room temperature in methanol and molar ratio of substrate/reagent/sulfur was 1/1/1
[b] Products are characterized by their physical constants and spectral analysis
[c] Yields refer to pure isolated products

ible groups are found to be unreactive under the reaction conditions. We believe that this method will present a better and more practical alternative to the existing methodologies and should find widespread application in organic synthesis.

Experimental

Materials were purchased from Fluka and Merck companies. The reactions were monitored by TLC using silica gel plates. Products were identified by comparison of their spectra and physical data with those of authentic samples [20, 23–27]. ^{1}H NMR spectra were measured at 90 and 500 MHz on a JEOL spectrometer with tetramethylsilane (Me_4Si) as an internal reference, and $CDCl_3$ as the solvent. IR spectra were recorded using an Alpha centauri FT-IR spectrophotometer. Elemental analysis was performed on a LECO 250 instrument; results agreed favorably with calculated values.

Preparation of N,N′-dibutyl-N,N,N′,N′-tetramethylethylenediammonium tetrahydroborate (BTMETB) ($C_{14}H_{42}B_2N_2$) *and N,N′-dibenzyl-N,N,N′,N′-tetramethylethylenediammonium tetrahydroborate (BZTMETB)* ($C_{20}H_{38}B_2N_2$)
An alkaline solution of sodium borohydride was prepared from 1.53 g $NaBH_4$ (0.04 mol) in 10 cm^3 5 *M* NaOH. Then, an aqueous solution of *N,N′*-dibutyl-*N,N,N′,N′*-tetramethylethylenediammonium bromide/chloride (5.00 g in 8 cm^3 H_2O) or *N,N′*-dibenzyl-*N,N,N′,N′*-tetramethylethylenediammonium bromide/chloride (5.00 g in 15 cm^3 H_2O) was added dropwise to the above solution at room temperature and stirred for 2 h. The resulting white solid product was filtered off, washed with ether, and dried in a vacuum desiccator over $CaCl_2$. The chemical formula of the reagents was established by IR and NMR spectra. The content of active reducing agent BH_4^- was determined by the titrimetric method [28].

BTMETB: ^{1}H NMR (500 MHz, D_2O): $\delta = -0.40$–0.10 (m, $J = 80.65$ Hz, 8H, BH_4^-), 0.92 (t, $J = 7.35$ Hz, 6H, CH_3), 1.35 (m, 4H, CH_2), 1.75 (m, 4H, CH_2), 3.17 (s, 4CH_3), 3.39 (t, $J = 8.5$ Hz, 4H, CH_2), 3.87 (s, 4H, CH_2) ppm; IR (KBr): $\bar{\nu} = 2973$, 2882, 2296, 2240, 1623, 1497, 1466, 1133, 986, 920 cm^{-1}.

BZTMETB: ^{1}H NMR (500 MHz, D_2O): $\delta = -0.40$–0.10 (m, $J = 80.6$ Hz, 8H, BH_4^-), 3.14 (s, 12H, CH_3), 3.97 (s, 4H, CH_2), 4.6 (s, 4H, CH_2), 7.52–7.59 (s, 10H, ArH); IR (KBr): $\bar{\nu} = 3034$, 2988, 2958, 2278, 2227, 1618, 1478, 1421, 1219, 1006, 880, 789, 733 cm^{-1}.

General procedure for preparation of alkyl and acyl disulfides
Sulfur powder (6 mmol) and quarternary diammonium tetrahydroborates (6 mmol) are thoroughly mixed in a two-neck 50 cm^3 round-bottomed flask bearing a condenser and a dropping funnel containing 10 cm^3 methanol. As the methanol is added to the solid mixture, an exothermic reaction takes place and the mixture is stirred at room temperature for 10–15 min. Then alkyl or acyl halide (6 mmol) was added and the reaction mixture stirred at room temperature for 3–5 min. When the color changed from red to faint yellow, the reaction was completed. The mixture was diluted with 40 cm^3 diethyl ether, and the suspension washed three times with water (3×15 cm^3). The organic layer was separated and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the dialkyl or diacyl disulfides. The pure solid products were obtained by recrystallization of dialkyl disulfides from ethanol and diacyl disulfides from 1,2-dichloroethane.

Dibenzyl disulfide (**2a**)
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.23$–7.79 (m, 10H, ArH), 3.60 (s, 4H, CH_2S) ppm; IR (KBr): $\bar{\nu} = 3051$, 2964, 2909, 708, 564, 465 cm^{-1}.

Bis(3-chlorobenzyl)disulfide (**2b**, $C_{14}H_{12}S_2Cl_2$)
Oil; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.12$–7.27 (m, 8H, ArH), 3.57 (s, 4H, CH_2S) ppm; IR (KBr): $\bar{\nu} = 3050$, 2920, 2890, 783, 690, 521 cm^{-1}.

Bis(4-chlorobenzyl)disulfide (**2c**) [20b]
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.36$–7.60 (q, 8.5 Hz, 8H, ArH), 3.81 (s, 4H, CH_2S) ppm; IR (KBr): $\bar{\nu} = 3080$, 2980, 2879, 679, 519, 464 cm^{-1}.

Bis(4-methoxybenzyl)disulfide (**2f**) [26]
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.0$–7.3 (m, 8H), 3.78 (2S, 6H, 2OCH3), 3.72 (2s, 4H, 2CH2*Ph*) ppm.

Diphenacyl disulfide (**2g**) [24]
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.38$–7.93 (m, 10H, ArH), 4.18 (s, 4H, CH_2S) ppm; IR (KBr): $\bar{\nu} = 3040$, 2955, 2893, 1690, 1578, 684, 574, 453 cm^{-1}.

Bis(1-naphthylmethylene)disulfide (**2h**, $C_{22}H_{18}S_2$)
Mp 147–149°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.24$–8.04 (m, 14H, ArH), 4.47 (s, 4H, CH_2S) ppm; IR (KBr): $\bar{\nu} = 3080$, 2980, 2879, 645, 579, 479 cm^{-1}.

Bis(cyclohexyl)disulfide (**2i**) [27]
^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.14$–1.34 (m, 10H), 1.55–1.63 (m, 2H), 1.72–1.80 (m, 4H), 1.97–2.03 (m, 4H), 2.61–2.69 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.66$, 26.05, 32.81, 49.91 ppm; IR (KBr): $\bar{\nu} = 2928$, 2852, 1447, 1260, 996 cm^{-1}.

Dibenzoyl disulfide (**2l**) [20a]
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.35$–7.70 (m, 10H, ArH) ppm; IR (KBr): $\bar{\nu} = 3047$, 1700, 1681, 674, 648, 440 cm^{-1}.

Bis(4-chlorobenzoyl)disulfide (**2m**) [20a]
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.44$–8.77 (q, $J = 8.63$, 8H, ArH) ppm; IR (KBr): $\bar{\nu} = 3118$, 1718, 1685, 634, 487 cm^{-1}.

Bis(3-chlorobenzoyl)disulfide (**2n**, $C_{14}H_8O_2S_2Cl_2$)
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.46$–8.02 (m, 8H, ArH) ppm; IR (KBr): $\bar{\nu} = 3060$, 1700, 1688, 720, 690, 507 cm^{-1}.

Bis(2-chlorobenzoyl)disulfide (**2o**) [20a]
^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 7.19$–7.64 (m, 8H, ArH) ppm. IR (KBr): $\bar{\nu} = 3109$, 1715, 1700, 642, 448 cm^{-1}.

Bis(4-methoxybenzoyl)disulfide (**2p**) [20a]
^{1}H NMR (80 MHz, $CDCl_3$): $\delta = 7.20$–7.69 (q, $J = 8.20$ Hz, 8H, ArH), 2.38 (s, 6H, $-OCH_3$) ppm; IR (KBr): $\bar{\nu} = 3116$, 2875–2960, 1718, 1685, 634, 487 cm^{-1}.

Acknowledgements

Financial support of this work from the Research Council of Mazandaran University is gratefully acknowledged.

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