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RESEARCH ARTICLE

$NaBH_4/S_8$/Wet neutral alumina; as an efficient reagent for facile synthesis of dialkyl disulfides under solvent free conditions

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Alkyl halides and tosylates were easily converted to their corresponding symmetrical dialkyl disulfide under solvent free mild reaction conditions using $NaBH_4/S_8$/wet neutral alumina in moderate to good isolated yields.

Keywords: Alkyl halide; Symmetrical dialkyl disulfide; Solvent free; Sulfur

1. Introduction

Dialkyl disulfides represent an interesting class of organosulfur compounds because they possess a unique and rich chemistry in the synthetic [1] and biochemical area [2]. Some naturally occurring disulfides such as ajoene and dysoxysulfone, found in garlic, onions and mahogany trees, have shown promise as antifungal, anticancer, and antithrombotic compounds [3]. Industrially, disulfides find wide applications as vulcanizing agents for rubbers and elastomers, giving those materials excellent tensile strength [4].

Symmetrical organic disulfides can be prepared by treatment of alkyl halide with disulfide anion and also indirectly by reaction of Bunte salts [5] with acid solution of iodide, thiocyanate, or thiourea or by treatment or pyrolysis with hydrogen peroxide [6]. Alkyl halides also give alkyl disulfides when they are refluxed with elemental sulfur and NaOH [4], $NaBH_4$ [7] and with piperidinium tetrathiotungstate or piperidinium tetrathiomolybdate [8]. Recently the synthesis of disulfide using thiourea under basic hydrogen peroxide condition has been reported [9]. Another route for the preparation of organic disulfides is oxidation of thiols and has been carried out with many oxidizing agents [10].

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Due to concerns about the environmental impact of chemical transformations, the search for alternative reaction media has become important area for investigation. As a part of this drive, solvent-free synthetic methods are being applied to a wide range of organic reactions [11]. Herein, and as an extension of our previous studies on application of solvent-free procedure in organic synthesis, especially in organosulfur chemistry [12–14] and due to the lack of any report on the preparation of disulfide under solvent free conditions, we wish to report the first solvent-less and remarkable fast method for the preparation of symmetrical organic disulfides.

2. Result and discussion

The reaction procedure is very simple and includes the addition of alkyl halides to the thoroughly ground mixture of $NaBH_4/S_8$/wet neutral alumina and grinding the resulting mixture for additional 5–20 minutes (scheme 1). A variety of structurally diverse alkyl or aryl alkyl halides and tosylates were applied to this reaction resulting to formation of corresponding symmetrical dialkyl disulfides in moderate to excellent yields. The results are summarized in table 1.

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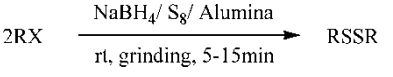

SCHEME 1

Initial experiments were done in the presence of silica gel as solid support, but low yield and purification problems encouraged the use of another inert inorganic solid support for this reaction. When wet neutral alumina was used instead of silica gel, the yield dramatically increased. One plausible explanation for this observation is the possibility of the chemical reaction between silica gel and alkyl halides, confirmed when benzyl chloride was treated with silica gel and ground for five minutes. After this time, only the 60% of the starting benzyl chloride was recovered. In addition, using graphite or clay as solid supports led to an extremely rapid, explosive reaction or very low yield besides the liberation of H_2S gas respectively. It should be noted that in the absence of inorganic solid supports no reactions was observed.

As clear from table 1, in the case of simple benzylic halides, (entries 1–3), the reactions proceed cleanly and very fast and produced desired disulfide in good yields but the presence of a nitro group on the aromatic ring (entry 9) lowered the yield. The low yield in this case can be attributed to the reduction of the nitro group during reaction progress. On the other hand, surprisingly, the nitrile groups (entries 7, 8) were not reduced or hydrolyzed under the conditions. Furthermore, the reaction was found to be general and applicable for primary alkyl halides (entries 4–6). The secondary and tertiary alkyl halides (entries 10, 12) did not afford desired disulfides even after an extended reaction period, or under microwave irradiation and phase transfer catalyst conditions [15, 16].

In another attempt, we examined this method for the large scale preparation of symmetrical disulfides. The results for preparation of *o*-bromo-benzyl disulfide as a model compound showed that this method can be easily applied for the large scale synthesis of this organo-sulfur compound.

As previously reported [7] and analogous to the reaction of elemental selenium with reducing agents [17]; we suggest that this reaction might be proceeding initially by formation of disulfide dianion (S_2^{2-}) [18–20] and in the second step this bidentate nucleophile reacted with alkyl halides to produced desired symmetrical disulfides.

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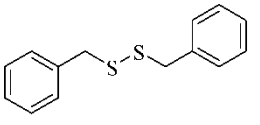
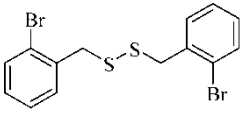
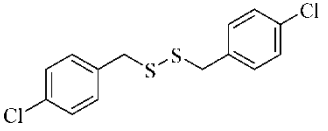
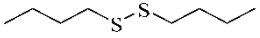
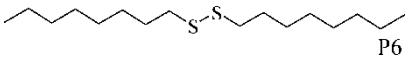
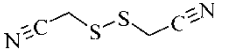
Table 1. The results for preparation of symmetrical disulfide using $NaBH_4/S_8$/alumina under solvent free conditions.

Entry	RX	Product[a]	RX/$NaBH_4/S_8$ mmole ratio	m.p. °C (lit)	Time (min)	Yield (%)[a]
1	Chloromethyl-benzene	 P1	2/2/0.25	69–71 (69–70)[15]	5	91
2	1-Bromo-2-chloromethyl-benzene	 P2	2/2/0.25	86–88 (87–88)[4]	5	92
3	1-Chloro-4-chloromethyl-benzene	 P3	2/2/0.25	60–62 (59–60)[4]	5	94
4	1-Bromo-butane	 P4	2/2/0.25	Liquid[16]	5	68
5	Toluene-4-sulfonic acid methyl ester	 P5	1/3/0.25	Liquid[16]	7	56
6	Toluene-4-sulfonic acid octyl ester	 P6	1/3/0.25	Oil[16]	5–7	80
7	Bromo-acetonitrile	 P7	1/2/0.25	Oil	<5	48

(continued)

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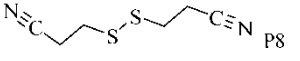
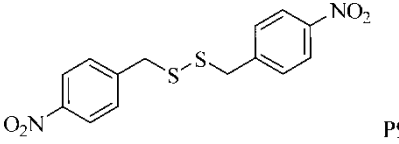
Table 1. Continued

Entry	RX	Product[a]	$RX/NaBH_4/S_8$ mmole ratio	m.p. °C (lit)	Time (min)	Yield (%)[a]
8	3-Bromo-propionitrile	 P8	1/2/0.25	Oil	<5	59
9	1-Bromomethyl-4-nitro-benzene	 P9	2/6/1.5	80–82 (83)[7]	15	20
10	Bromodiphenylmethane	No Reaction	1/8/0.5	–	15	–
11	Chlorotriphenylmethane	No Reaction	1/8/0.5	–	15	–

[a]All products were identified by their IR and NMR spectral data and comparison of their mp with published data.
[b]Isolated pure product.

The present solvent free procedure provides an efficient and very simple methodology for the preparation of symmetrical disulfides using elemental sulfur as a very cheap and safe disulfide anion source with good yields under mild conditions. Finally, simplicity in operation (set-up and work-up process), giving good yields for large-scale reactions, and having a green reaction conditions makes this method as an attractive alternative for synthesis of symmetrical disulfides.

3. Experimental

3.1 *General*

Products were characterized by comparison of their spectroscopic data (^{1}H NMR, IR) with those reported in the literature. All yields refer to isolated products. The products were purified by column chromatography or preparative TLC using SiO_2 as stationary phase. The FTIR spectra of neat samples between NaCl disks were obtained on a BOMEM 450 instrument. The high-field NMR spectra were obtained on a Brucker AC 400 MHz. ^{1}H and ^{13}C chemical shifts are quoted relative to solvent resonance(s) as internal standard.

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3.2 *General procedure for synthesis of symmetrical disulfides*

To the thoroughly ground mixture of wet neutral Al_2O_3 (1 g), $NaBH_4/S_8$ (molar ratio according to the table 1), appropriate amounts of alkyl halides or tosylates (according to the table 1), were added and the resulting reaction mixture was ground in a mortar for several minutes. After the completion of the reaction (TLC monitoring), the pure product was extracted with CH_2Cl_2. The solvent was removed under reduced pressure to afford the product, in almost pure form, which was further purified by column chromatography on silica gel (hexane: ethyl acetate, 9:1).

3.3 *Typical procedure for large-scale synthesis of o-bromobenzyl disulfide*

To the thoroughly ground mixture of wet neutral Al_2O_3 (20 g), $NaBH_4$ (80 mmol), and S_8 (5 mmol) the 1-bromo-2-chloromethyl-benzene (20 mmol), were added and the resulting mixture ground in a mortar for 15 minutes. After the completion of the reaction (TLC monitoring), the pure product was extracted with CH_2Cl_2. The solvent was removed under reduced pressure to afford the product, in almost pure form which was further purified by column chromatography on silica gel (yield: 89%).

3.4 *Spectroscopic data of some selected compounds*

3.4.1 Compound P7. IR (neat NaCl disk, cm^{-1}) 2957, 2870, 2261, 1518, 1547, 1337, 1273, 907, 492; ^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K) $\delta = 4.2$ (s, 4H, SCH_2) ^{13}C NMR (100.6 MHz, $CDCl_3$, 300 K) $\delta = 24.2$, 120.7.

3.4.2 Compound P8. IR (neat NaCl disk, cm^{-1}) 2957, 2870, 2257, 1678, 1539, 1447, 1221, 813, 559, 419; ^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K) $\delta = 2.75$–2.78 (t, 4H, SCH_2); 2.97–2.99 (t, 4H, CH_2) ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 20.1$, 37.2, 11.6.2.

3.4.3 Compound P9. IR (KBr, cm^{-1}): 3080, 2872, 1619, 1503, 1476, 622, 539, 473; ^1H NMR (400.1 MHz, $CDCl_3$, 300 K): $\delta = 3.6$ (s, 4H, SCH_2); 7.29 (d, 4H, Ar−H); 8.17 (d, 4H, Ar−H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 300 K) $\delta = 43.1$, 126.2, 130.3, 131.3, 132.6, 139.4, 140.9.

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