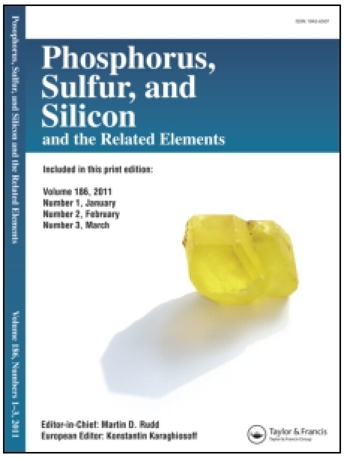

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Facile Solvent-Free Generation of Disulfide Dianion and its Use for Preparation of Symmetrical Disulfides

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Facile Solvent-Free Generation of Disulfide Dianion and its Use for Preparation of Symmetrical Disulfides

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A variety of symmetrical dialkyl disulfides were prepared from the reaction of alkyl halides, sodium hydroxide and elemental sulfur under solvent free conditions. The reaction proceeded very fast and produced the desired products in moderate to excellent isolated yields.

Keywords Alkyl halide; solvent free; sulfur; symmetrical dialkyl disulfides

INTRODUCTION

Dialkyl disulfides are an important class of compounds and have received considerable attention in the literature. They are of interest due to both: numerous biological properties[1] and a rich synthetic organic chemistry.[2] The most common routes for the preparation of organic disulfides are the oxidation of thiols, which has been carried out with many oxidizing agents,[3] as well as various alkylation methods using sulfur nucleophiles including sulfur/NaOH in refluxing methanol,[4] sulfur/NaOH/phase transfer catalyst under microwave irradiation, sulfur/$NaBH_4$,[5] piperidinium tetrathiotungstate or piperidinium tetrathiomolybdate,[6] and Bunte salts. [7] However, despite the availability of many preparative procedures the restrictions

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that accompany some of them, make new, mild, and practical methods highly desirable.

RESULTS AND DISCUSSION

In continuation of our investigations on new methodologies for the synthesis of organo-sulfur compounds,[8] we recently published the first solvent-free preparation of symmetrical organic disulfides under conventional conditions using $NaBH_4/S_8$/wet neutral alumina.[9] Here, we report a revised procedure for a reproducible and scalable preparation of dialkyl disulfides in high yields using S_8/NaOH in the presence of silica gel as solid support under solvent free conditions (Scheme 1). The reaction procedure is very simple and includes the generation of the disulfide anion under microwave irradiation and then the grinding of the resulted dianion with an appropriate alkylating agent.

The scope and limitations of this transformation were determined by the synthesis of several structurally diverse dialkyl disulfides from the corresponding alkyl halides under our reaction conditions. The reaction is generally fast, requiring from 5 to 10 min for completion in most of the cases. Reduced rates were observed with secondary alkylating agents, such as cyclohexyl tosylate. Tertiary alkyl halides did not afford the desired disulfides even after longer reaction times, or under microwave irradiation. In addition the generation of the S^{2-} dianion can be performed under conventional heating (oil bath, 70–80°C) in the less than 20 min; at room temperature, the disulfide dianion was not formed at all.

As previously reported,[4] we suggest that this reaction proceeds via the disulfide dianion (S_2^{2-}), which is formed in the first step. In the second step, the S^{2-} dianion reacts with the respective alkyl halide to produce the corresponding symmetrical disulfide.

In conclusion, the procedure described here is operationally simple and allows a rapid and high-yielding conversion of alkyl halides and alkyl tosylates to the corresponding symmetrical disulfides under very

$$2\ \mathrm{RX} \xrightarrow[\text{grinding, rt, 5-30 min}]{\mathrm{S_8/NaOH/silica\ gel}} \mathrm{RSSR}$$

X: Cl, Br, OTs

SCHEME 1

mild conditions. The method seems to be more convenient with respect to other reports and can be used as a valid alternative to other methods, so avoiding tedious purifications or the use of more toxic reagents.

EXPERIMENTAL

General

Products were characterized by comparison of their spectroscopic data (^{1}H and ^{13}C NMR, IR) with those reported in the literature. All yields refer to isolated products. The reactions were done in BUTANE microwave oven. The FT-IR 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 instrument. ^{1}H and ^{13}C chemical shifts are quoted relative to solvent resonance(s) as internal standard.

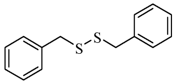
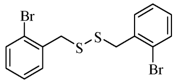
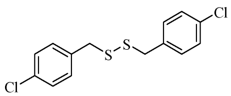
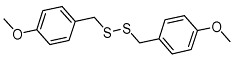
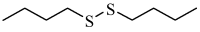
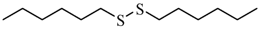
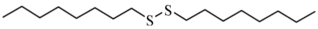
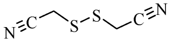
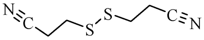
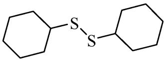
General Procedure for Synthesis of Symmetrical Disulfides

The mixture of 3 mmol S_8 and 3 mmol NaOH was exposed to microwave irradiation in domestic microwave oven for 3 minutes at a power of 200 W. Subsequently 1 mmol of the appropriate alkyl halide or tosylate and 0.5 g of silica gel were added and the resulting mixture ground in a mortar for the appropriate time (according to Table I). After completion of the reaction (monitored by TLC), 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).

Typical Procedure for the Large-Scale Synthesis of *o*-Bromo-Benzyl Disulfide

A mixture of S_8 (60 mmol) and NaOH (60 mmol) was exposed to microwave irradiation in a domestic microwave oven for 3 minutes at the appropriate power of the microwave oven (200 W). Subsequently, 1-bromo 2-chloromethyl benzene (20 mmol) and 0.5 g of silica gel were added and the resulting mixture was ground in a mortar for the appropriate time (according to Table I). After completion of the reaction (monitored by TLC), the product was extracted with CH_2Cl_2. The solvent was removed under reduced pressure to afford the disulfide in almost pure form. It was further purified by column chromatography on silica gel (hexane/ethyl acetate 9:1).

TABLE I Preparation of Symmetrical Disulfides Using S_8/NaOH

RX	Product[a]	M.p. °C (lit)	(min) (min)	Yield (%)[a]
Chloromethyl-benzene		69–71(69–70)[10]	3	92
1-Bromo-2-chloromethyl-benzene		86–88 (87–88)[4]	3	90
1-Chloro-4-chloromethyl-benzene		60–62 (59–60)[4]	3	94
1-Bromomethyl-4-methoxy-benzene		75–78 (76–80)[10]	5	87
1-Bromo-butane		Liquid[11]	30	68
1-Bromo-hexane		Oil[11]	10	72
Toluene-4-sulfonic acid octyl ester		Oil[11]	10	90
Bromo-acetonitrile		Oil[9]	5	65
3-Bromo-propionitrile		Oil[9]	5	67
Toluene-4-sulfonic acid cyclohexyl ester		127–130 (125–130)[12]	15	65
Chlorotriphenylmethane	No Reaction	—	15	—

[a] All products were identified by their IR and NMR spectral data and comparison of their m.p. with published data; and [b] isolated pure product.

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