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ORIGINAL PAPER

Synthesis of sulfides under solvent- and catalyst-free conditions

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Abstract A simple, highly efficient, and green protocol has been developed for preparation of sulfides from alkyl or aryl thiols and benzyl-, allyl-, *t*-butyl, and adamantyl halides under solvent- and catalyst-free conditions.

Keywords Neat · Solvent-free · Catalyst-free · Sulfides · Thiols

Introduction

In practice, from an ecological point of view, the best solvent is without a doubt no solvent. There are of course a great many reactions that can already be carried out in the absence of solvent. Reports on solvent-free reactions have, however, become increasingly frequent and specialized over the past few years. The field of solvent-free organic synthesis covers all branches of organic chemistry. It includes stochiometeric solid–solid reactions [1] and gas–solid reactions [2], and supported inorganic reagents [3], which in many cases are accelerated or even made possible through microwave irradiation [4]. There are also reactions in which at least one reactant is liquid under the conditions employed, which means that the solvent that would normally be used can simply be left out.

As part of our research to develop practical, simple, and green methodologies in organic synthesis, we report here a convenient route to the preparation of benzyl sulfides of general formula *Ph*CH_2SR through a simple coupling of thiols with benzyl halides under solvent- and catalyst-free conditions.

Sulfides are a class of important synthetic reagents and intermediates in organic, medicinal, bio-organic, and heterocyclic chemistry [5–7]. Also, they are the starting compounds for the preparations of other sulfur compounds, such as sulfoxides, sulfones, and sulfonium compounds, etc. [8]. Numerous procedures exist for the preparation of sulfides, including desulfurization of disulfides, aryllithium or organocuprate addition to thiocarbonyl compounds, reduction of sulfoxides and sulfones [9, 10]; nucleophilic displacement of aryl and alkyl halides by thiolate ion [11–13]; treatment of thiols and alkyl halides with *DBU* [14], or cesium carbonate and tetrabutylammonium iodide [15]; the treatment of alkyl halides with sodium sulfide [16], thiourea [17], or thiocarbonate [18]; the reaction of halides with thiosilanes [19]; ring-opening of epoxides with thiols [20], and disulfides [21]; Michael addition of thiols [22] and disulfides [23] to α,β-unsaturated carbonyl compounds; intermolecular *S*-alkylation of thiols with alcohols [24]; the reaction of thiolate anions, generated in situ by indium(I) iodide promoted cleavage of dialkyl/diaryl disulfides, with styrenes [25]. Because of various disadvantages such as use of hazardous and toxic solvents, difficulty in recovery of high boiling solvents, use of costly catalysts, etc., encountered in the reported methodologies, we decided to develop a more convenient and eco-friendly method.

Results and discussion

In order to optimize the reaction condition with respect to temperature, and time, we first studied the reaction of thiophenol (1.1 mmol) with benzyl bromide (1.0 mmol) as a model reaction in the absence of catalyst under neat

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$$\text{PhSH} + \text{PhCH}_2\text{Br} \xrightarrow[\Delta]{\text{neat}} \text{PhSCH}_2\text{Ph}$$

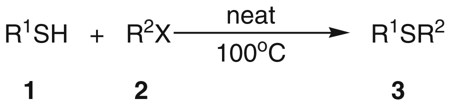
Scheme 1

Table 1 Reaction of thiophenol with benzyl bromide at various temperatures

Entry	Temperature (°C)	Time (h)	Yield (%)[a]
1	50	13	53
2	50	23	72
3	70	19	73
4	90	10	74
5	100	16	96

Molar ratios of thiophenol:benzyl bromide = 1.1:1

[a] Isolated yield



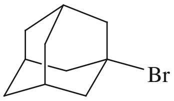
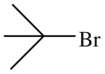
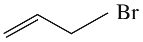
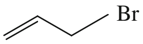
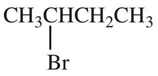
$$\underset{\mathbf{1}}{\text{R}^1\text{SH}} + \underset{\mathbf{2}}{\text{R}^2\text{X}} \xrightarrow[100^\circ\text{C}]{\text{neat}} \underset{\mathbf{3}}{\text{R}^1\text{SR}^2}$$

Scheme 2

conditions at various temperatures (Scheme 1). As revealed in Table 1, the best result was obtained at 100 °C. Therefore, we decided to perform our study at thiol:halide at 1.1:1 at 100 °C to afford the corresponding sulfides in moderate to excellent yields (Scheme 2). Representative results are summarized in Table 2. The product isolation with very high purity was easily achieved by subjecting the crude reaction mixture to preparative TLC.

A series of thiols (both aromatic and aliphatic) were treated with various halides to afford the corresponding sulfides. The best results were obtained from the reaction of aromatic thiols and benzyl halides. Benzyl sulfides prepared from aromatic thiols (entries 1–6 and 12–15, Table 2) generally give higher yields than those produced from aliphatic thiols (entries 7–11, Table 2). Comparing the reactions between thiols and benzyl chloride (entries 14 and 15, Table 2) with those of benzyl bromide (entries 4 and 5, Table 2) clearly shows longer reaction times and lower yields for benzyl chloride. In the case of the reaction of aliphatic thiols of increasing chain length, e.g., butane, hexane, and octane (entries 9–11, Table 2), the yield of the product increases with the increase in the length of the alkyl chain. This may be attributed to the increase in the electron-releasing capacity—and hence nucleophilicity—with increasing length of the chain. In general, compared to aromatic thiols, aliphatic thiols gave lower yields (entries 7–11, Table 2). While treatment of thiols with 1-adamantyl-, *t*-butyl, and allyl bromide gives the corresponding sulfides in moderate yields (entries 16–19, Table 2), primary and secondary aliphatic halides do not react with thiols and remain mostly intact after the typical reaction times (entries 20 and 21, Table 2).

Table 2 Synthesis of sulfides **3** under solvent- and catalyst-free conditions at 100 °C

Entry	*R*^{1}	*R*^{2}X	Time (h)	Yield (%)[a,b]
1	4-BrC$_6$H$_4$	*Ph*CH$_2$Br	8	80[15]
2	4-CH$_3$C$_6$H$_4$	*Ph*CH$_2$Br	16	90[26]
3	2-Naphthyl	*Ph*CH$_2$Br	32	86[27]
4	*Ph*	*Ph*CH$_2$Br	16	96[26]
5	4-ClC$_6$H$_4$	*Ph*CH$_2$Br	12	92[26]
6	4-CH$_3$OC$_6$H$_4$	*Ph*CH$_2$Br	22	82[28]
7	*Ph*CH$_2$	*Ph*CH$_2$Br	28	66[26]
8	HOCH$_2$CH$_2$	*Ph*CH$_2$Br	11	78[15]
9	*n*-C$_4$H$_9$	*Ph*CH$_2$Br	39	30[28]
10	*n*-C$_6$H$_{13}$	*Ph*CH$_2$Br	38	53[28]
11	*n*-C$_8$H$_{17}$	*Ph*CH$_2$Br	38	61[28]
12	4-CH$_3$OC$_6$H$_4$	*Ph*CH$_2$Br	28	77[28]
13	4-ClC$_6$H$_4$	4-NO$_2$C$_6$H$_4$CH$_2$Br	30	83[29]
14	4-ClC$_6$H$_4$	*Ph*CH$_2$Cl	18	87[26]
15	*Ph*	*Ph*CH$_2$Cl	19	81[26]
16	*Ph*		30	62[30]
17	4-CH$_3$C$_6$H$_4$		20	65
18	4-ClC$_6$H$_4$		19	58[31]
19	*Ph*		19	52[31]
20	*Ph*	CH$_3$(CH$_2$)$_4$CH$_2$Br	40	–
21	4-CH$_3$C$_6$H$_4$	 $\underset{\text{Br}}{\text{CH}_3\text{CHCH}_2\text{CH}_3}$	40	–

[a] Yields refer to those of pure isolated products characterized by ^{1}H and ^{13}C NMR spectroscopy

[b] References for known compounds

In summary, we have developed a simple and efficient procedure for preparation of sulfides. This solvent- and catalyst-free reaction is very useful both from economical and environmental points of view. This protocol offers some advantages over procedures reported earlier in that it avoids the use of hazardous organic solvents, toxic and expensive reagents, as well as operational simplicity, high yields of products, and low costs.

Experimental

Chemicals were purchased from Merck chemical company. Yields refer to isolated products. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using a Bruker AQS-300 Avance spectrometer. IR spectra were obtained using an ABB FTLA 2000 instrument.

Typical procedure exemplified by the preparation of benzyl phenyl sulfide (Entry 4, Table 2, $C_{13}H_{12}S$)

In a typical experiment, a mixture of thiophenol (1.1 mmol, 121 mg) and benzyl bromide (1.0 mmol, 171 mg) was magnetically stirred in a test tube at 100 °C for 16 h. After completion of the reaction, as indicated by TLC, the crude mixture was cooled and subjected to preparative TLC (silica gel, eluent *n*-hexane) to obtain 191 mg of the pure benzyl phenyl sulfide (96%) as colorless crystals. M.p.: 41–42.5 °C (lit. [26] 41–42 °C). ^{1}H NMR ($CDCl_3$): $\delta = 4.17$ (s, 2H, CH_2), 7.22–7.38 (m, 10H, Ph) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 39.0$, 126.3, 127.2, 128.5, 128.9, 129.8, 136.4, 137.5 ppm [27–31].

This procedure is followed for all the reactions listed in Table 2. All products are known compounds and were identified by spectroscopic data (^{1}H and ^{13}C NMR) that are in good agreement with those reported (references in Table 2).

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