

## A Novel Method of Preparing Unsymmetrical Thioether from Disulfides

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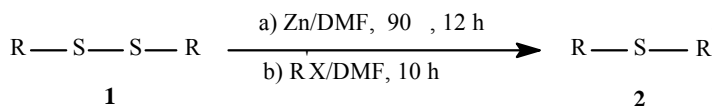
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**Abstract:** The disulfides reacted with zinc in DMF, followed by alkyl halides, giving unsymmetrical thioether in excellent yields. This reaction takes place under mild and neutral conditions.

**Keywords:** Unsymmetrical thioethers, zinc, alkyl halides, disulfides.

Aryl, alkenyl and alkyl thioether are important synthetic reagents and intermediates in organic synthesis<sup>1</sup>. They have been widely employed in the synthesis of novel biologically active compounds<sup>2</sup>, polymer materials<sup>3</sup> and used as extracting reagents<sup>4</sup>. Many methods for the synthesis of unsymmetrical thioethers have been reported, and the most common approach is use of thiol, which reacted with alkyl halides under basic condition<sup>5,6</sup> by nucleophilic substitution reaction. Unsymmetrical thioether can also be obtained from the electrophilic addition reaction of thiol with alkene<sup>7</sup>, from Micheal addition<sup>8</sup>, or from the thermolysis of dialkyl disulfides at high temperature<sup>9</sup>. However, these methods have shortages, such as foul smell of thiol, strong basic condition, requiring high temperature or need precious metal. Herein we wish to report a new simple and efficient method for the conversion of the symmetrical disulfides to the corresponding unsymmetrical thioethers by Zn/DMF system under mild and neutral conditions.

Scheme 1



### Experimental

IR spectra were measured on a Nicolin NEXUS 670 spectrophotometer. Elemental Analysis was carried out with Elementar Vario EL analyzer. Mass spectra were performed by a Agilent instrument. <sup>1</sup>H NMR spectra were obtained on a Bruker Avance 400MHz spectrometer. Metallic zinc was activated before use referring to

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literature<sup>10</sup>. The DMF was freshly distilled and dried *prior* to use..

**Table 1** Yields of products

Compd.	R	R'	Yield (%) <sup>*</sup>
<b>2a</b>	PhCH <sub>2</sub>	CH <sub>3</sub> CH <sub>2</sub>	88
<b>2b</b>	PhCH <sub>2</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	87
<b>2c</b>	PhCH <sub>2</sub>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	83
<b>2d</b>	<i>p</i> -ClPhCH <sub>2</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	82
<b>2e</b>	<i>p</i> -ClPhCH <sub>2</sub>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	77
<b>2f</b>	<i>p</i> -ClPhCH <sub>2</sub>	PhCH <sub>2</sub>	91
<b>2g</b>	<i>p</i> -CH <sub>3</sub> OPhCH <sub>2</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	82
<b>2h</b>	<i>p</i> -CH <sub>3</sub> OPhCH <sub>2</sub>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	79
<b>2i</b>	<i>p</i> -CH <sub>3</sub> OPhCH <sub>2</sub>	PhCH <sub>2</sub>	86

\* isolated yields

### General procedure

In a 25 mL three-necked glass flask equipped with a condenser and magnetic stirring bar under dried nitrogen atmosphere were placed zinc powder (2.5 mmol), disulfide (1 mmol), dried DMF (6 mL) and a small amount of I<sub>2</sub> were added subsequently. The resulting mixture was stirred at 90°C for 12 h, until the color of the mixture changed from gray to white. Then alkyl halide (2.5 mmol) in DMF (2 mL) was added through a syringe. The resulting mixture was stirred for 10 h, and dilute HCl (5 %, 15 mL) was added to quench the reaction. After extraction with ether (15 mL×3), the organic layer was washed with water (20 mL) and dried over anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was then purified by preparative TLC on silica gel (cyclohexane: ethyl acetate = 9.5: 0.5 as eluent) to give pure product. The analytical data of the products **2a-e** are identical with those reported in reference<sup>11</sup>. The products **2f-i** are new compounds and their physical data are given in the notes<sup>12</sup>.

In conclusion, we have presented a novel method for the synthesis of unsymmetrical thioethers from disulfides by Zn/DMF/R'X system. The method reported here avoids release of foul smell of thiol, and uses easily available starting materials. The reaction requires mild reaction conditions and gives excellent yield (77-91 %) of the products.

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12. **2g**: clear yellowish liquid,  $^1\text{H NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 0.90 (t, 3H,  $J=7.33\text{Hz CH}_3$ ), 1.39-1.56 (m, 4H,  $\text{CH}_2$ ), 2.42 (t, 2H,  $J=7.33\text{Hz SCH}_2-$ ), 3.68 (s, 2H,  $-\text{CH}_2\text{S}$ ), 3.80 (s, 3H,  $\text{OCH}_3$ ), 6.85-7.24 (m, 4H, Ar-H). IR(KBr/ $\text{cm}^{-1}$ ): 3000, 2931, 2835, 1610, 1511, 1464, 1250, 1036, 830. Anal Calcd. for  $\text{C}_{12}\text{H}_{18}\text{OS}$ : C, 68.52; H, 8.63; S, 15.52; Found: C, 68.38; H, 8.37; S, 15.50. EI-MS:  $m/z$  210.0, 121.0(base), 91, 78. **2h**: clear yellowish liquid,  $^1\text{H NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 0.89(t, 3H,  $J=7.07\text{Hz, CH}_3$ ), 1.24-1.39(m, 6H,  $\text{CH}_2$ ), 1.52-1.60(m, 2H,  $\text{SCH}_2\text{CH}_2-$ ), 2.41(t, 2H,  $J=7.33\text{Hz, SCH}_2-$ ), 3.67(s, 2H,  $-\text{CH}_2\text{S}$ ), 3.80(s, 3H,  $\text{OCH}_3$ ), 6.85-7.24 (m, 4H, Ar-H). IR(KBr/ $\text{cm}^{-1}$ ): 3010, 2927, 2855, 1610, 1510, 1464, 1249, 1037, 829. Anal Calcd. for  $\text{C}_{14}\text{H}_{22}\text{OS}$ : C, 70.54; H, 9.30; S, 13.45; Found: C, 70.52; H, 9.20; S, 13.55. EI-MS:  $m/z$  238.0, 121.0(base), 91, 28, 41. **2i**: clear liquid,  $^1\text{H NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 3.59 (s, 2H,  $\text{SCH}_2-$ ), 3.62 (s, 2H,  $-\text{CH}_2\text{S}$ ), 3.83(s, 3H,  $\text{OCH}_3$ ), 6.87-7.32 (m, 9H, Ar-H). IR (KBr/ $\text{cm}^{-1}$ ): 3028, 2952, 2834, 1609, 1510, 1453, 1248, 1035, 833. Anal Calcd. for  $\text{C}_{15}\text{H}_{16}\text{OS}$ : C, 73.73; H, 6.60; S, 13.12; Found: C, 73.52; H, 6.43; S, 13.30. EI-MS:  $m/z$  244.0, 121.0(base), 91, 77, 65, 45.

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