# **Communications**

## Synthesis of Disulfides by **Copper-Catalyzed Disproportionation of** Thiols

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Transformation of thiols to disulfides is important from both synthetic and biochemical points of view and accordingly numerous studies have been reported.<sup>1-10</sup> It is commonly carried out by chemical oxidation utilizing various oxidizing agents such as molecular oxygen,<sup>2</sup> metal ion,<sup>3</sup> metal oxide,<sup>4</sup> DMSO,<sup>5</sup> nitric oxide,<sup>6</sup> halogen<sup>7</sup> and sodium perborate.8 Electrochemical oxidation also have recently been applied successfully for the disulfide synthesis.<sup>9,10</sup> On the other hand, borohydride exchange resin (BER)-transition metal salts systems such as BER- $CuSO_4$ ,<sup>11</sup> and BER-Ni(OAc)<sub>2</sub><sup>12</sup> have been proved to be valuable selective reducing systems for  $\alpha,\beta$ -unsaturated carbonyl compounds, halides, azides and nitro compounds. In the course of these studies, we have found the copper deposited on BER by reduction of CuSO<sub>4</sub> with BER is an efficient catalyst for the disproportionation of thiols to disulfides and hydrogen.<sup>13,14</sup> We report here a new synthesis of disulfides by disproportionation of thiols.

The procedure is very simple.<sup>15</sup> Catalyst is prepared on the borohydride exchange resin (BER) in methanol by reducing a catalytic amount (0.01 equiv) of  $CuSO_4$  with BER, and hydride was destroyed by refluxing methanol for 3 h. Thiols were transformed to the corresponding disulfides over this catalyst quantitatively under nitrogen at room temperature. As shown in Table 1, primary and





secondary thiols were readily transformed to disulfides in 3 h at room temperature (entries 1-4 and 6); however, the more bulky thiol, 1,1-dimethylethanethiol, required 6 h, presumably due to steric reasons (entry 5). Functional groups such as carbon-carbon double bond (entry 7), hydroxy (entries 8 and 9), amino (entries 10 and 15), ester (entries 11 and 15), and furan (entry 12) did not interfere in the disulfide synthesis. Aromatic thiols, benzenethiol and 2-mercaptopyridine, required 6 and 9 h, respectively; however, the latter reaction could be completed in 6 h by introducing a stream of nitrogen (entries 13 and 14). The removal of hydrogen from the system presumably accelerated the reaction. Indeed we observed only 19% reaction of hexanethiol in 3 h under 1 atm hydrogen (entry 2). Finally, the cysteine methyl ester was also transformed smoothly to cystine dimethyl ester in 3 h (entry 15).

We did several studies on the catalyst<sup>16</sup> using hexanethiol, and the results are summarized in Table 2. As shown in Table 2, the reaction could be adequately completed in 3 h over 0.01 equiv of copper on 0.5 equiv of BER at room temperature (standard condition). Interestingly, the reaction was sluggish at 65  $^{\circ}\mathrm{C}$  showing only 25% formation of disulfide (entry 1). When the remaining hydride of BER was not destroyed by refluxing of methanol solution for 3 h, the disproportionation required longer reaction time (entry 2). Presumably the evolution of hydrogen gas inhibits the reaction. The rate of disproportionation is not so sensitive to the amount of copper (entries 1 and 3), but seems to be influenced by the surface area of catalyst; the copper (0.01 equiv)

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(13) The disproportionation of thiol to disulfide and hydrogen is reported unfavorable thermodynamically (2 CH<sub>3</sub>SH (l) = CH<sub>3</sub>SSCH<sub>3</sub>.

<sup>(1)</sup> The disproprior of the of the distribution of the distributio believe, the escape of H<sub>2</sub> gas from the system should have favored the disproportionation in our system.

<sup>(14)</sup> In the disproportionation of hexanethiol, approximately 0.95 equiv of hydrogen was collected and analyzed with GLPC using a molecular sieve column.

<sup>(15)</sup> Preparation of borohydride exchange resin: An aqueous solution of sodium borohydride (1 M, 500 mL) was stirred with wet chlorideform anion exchange resin (Amberlite IRA-400 [20-50 mesh], 200 g) for 15 min. The resulting resin was washed thoroughly with distilled water until free from excess NaBH<sub>4</sub>. The borohydride form anion exchange resin was then dried in vacuo at 60 °C for 5 h to give 102 g of dried borohydride exchange resin (BER). The dried resin was analyzed for borohydride content by hydrogen evolution on acidification with 2 N HCl, and the average hydride content of BER was found to be 3.0 mmol of  $BH_{4^-}$  per gram. The dried resin was stored under nitrogen in refrigerator (~4 °C). The hydride content was constant over 6 weeks. General procedure for preparation of disulfides: The preparation of dibutyl disulfide is representative. A solution of  $CuSO_{4}$  (0.025 g, 0.1 mmol) in methanol (50 mL) was added to the BER (1.67 g, 5 mmol), and the mixture was stirred under reflux for 3 h. The mixture was cooled to room temperature under nitrogen. After adding a solution of butanethiol (0.90 g, 10 mmol) in methanol (10 mL), the reaction mixture was stirred at room temperature for 3 h. Complete reaction was confirmed by GLPC, and the resin was removed by filtration. Methanol was evaporated under reduced pressure to give pure dibutyl disulfide (0.87 g, 98%)

<sup>(16)</sup> The Cu on BER was reused for two times without any change of activity, but the third reaction required longer reaction time (5 h). And the activity of catalyst was sensitive to air. Thus  $18\ h$  was required for the complete reaction when the catalyst was exposed to air for 1 h.

Table 1.	Synthesis of Disulfides from '	Thiols by Copper-	-Catalyzed	l Disproportionation in Methanol at Roc	m			
Temperature <sup>a</sup>								

entry	substrate	product	time (h)	yield (%)
1	butanethiol	dibutyl disulfide	3	98
2	hexanethiol	dihexyl disulfide	3	$98 (19)^b$
3	sec-butanethiol	di-sec-butyl disulfide	3	97
4	cyclohexanethiol	dicyclohexyl disulfide	3	99
5	1,1-dimethylethanethiol	di-tert-butyl disulfide	6	96
6	a-toluenethiol	dibenzyl disulfide	3	97
7	cinnamyl mercaptan	dicinnamyl disulfide	3	97
8	2-mercaptoethanol	bis(2-hydroxyethyl) disulfide	3	98
9	2-hydroxycyclohexanethiol	bis(2-hydroxycyclohexyl) disulfide	3	95
10	2-aminoethanethiol	bis(2-aminoethyl) disulfide	3	98
11	ethyl 2-mercaptopropionate	bis[1-(ethoxycarbonyl)ethyl] disulfide	3	96
12	2-(mercaptomethyl)furan	difurfuryl disulfide	3	96
13	benzenethiol	diphenyl disulfide	6	97
14	2-mercaptopyridine	di-2-pyridyl disulfide	9 (6) <sup>c</sup>	94 (98) <sup>c</sup>
15	L-cysteine methyl ester	L-cystine dimethyl ester	3	96

<sup>a</sup> 10 mmol of thiols were reacted over the copper catalyst prepared by the reduction of 0.1 mmol of CuSO<sub>4</sub> with 5.0 mmol of BER. <sup>b</sup> Under 1 atm hydrogen. <sup>c</sup> Under a stream of nitrogen.

Table 2. Comparison of the Catalysts for the Disproportionation of Thiol to Disulfide at Room

Temperature							
entry	hydride <sup>b</sup>	metal salt <sup>b,c</sup>	time (h)	yield (%) <sup>d</sup>			
1	BER (0.5)	CuSO <sub>4</sub> (0.01)	1	80			
			3	$100(25)^{e}$			
$2^{f}$	BER (0.5)	$CuSO_4(0.01)$	3	7			
			<b>24</b>	62			
3	BER (0.5)	$CuSO_{4}(0.1)$	1	82			
			3	100			
4	BER (3.0)	$CuSO_{4}(0.01)$	1	100			
5	BER (3.0)	$Ni(OAc)_2(0.01)$	1	43			
			3	70			
6	BER (3.0)	$Co(OAc)_2(0.01)$	1	86			
			3	100			
7	$NaBH_{4}(3.0)$	$CuSO_{4}(0.01)$	1	41			
			6	94			
			9	100			
8	NaBH4 (3.0) <sup>g</sup>	$CuSO_4(0.01)$	1	61			
			3	87			
			6	100			
9		$Cu^h$	3	5			

<sup>a</sup> Hexanethiol was used. <sup>b</sup> Millimoles per millimole of thiol. <sup>c</sup> Catalysts were prepared by reducing the metal salt with hydride and destroying the remaining hydride by refluxing for 3 h in methanol. <sup>d</sup> Yield of dihexyl disulfide. <sup>e</sup> At 65 °C. <sup>f</sup> The BER was not destroyed. <sup>g</sup> Silica gel (1.0 g per mmol of thiol) was added as a support. <sup>h</sup> Copper powder or activated copper.<sup>17</sup>

deposited on 3 equiv of BER is more efficient than the same amount of copper on 0.5 equiv of BER (entries 1 and 4). Nickel boride and cobalt boride on BER were also effective catalysts, but required longer reaction time (entries 5 and 6). Similarly, copper catalyst prepared by NaBH<sub>4</sub>, either with or without silica gel, was less effective

than the catalyst prepared by BER-CuSO<sub>4</sub> (entries 7 and 8). We also carried out the same reaction over copper powder or the activated copper catalyst prepared by the method of Vogel;<sup>17</sup> however, both reactions were very sluggish giving only 5% of disulfide in 3 h (entry 9). These results suggest that the copper catalyst prepared by the reduction of CuSO<sub>4</sub> with BER in methanol must be specially active for the disproportionation of thiols.

In an attempt to understand the reaction, we carried out two reactions using a equimolar mixture of hexanethiol and styrene. Thus one reaction over the present catalyst at the standard condition gave dihexyl disulfide exclusively, and styrene remained unreacted. However another reaction, which was carried out with 0.1 equiv of AIBN in refluxing methanol, proceeded to give 2-phenethyl hexyl sulfide in 65% yield without contamination with dihexyl disulfide. This strongly suggests that the copper-catalyzed disproportionation does not involve radical intermediates. This was also confirmed with the quantitative formation of dicinnamyl disulfide (Table 1, entry 7).

In conclusion, our work provides a simple synthetic method for synthesis of disulfides from the corresponding thiols, in essentially quantitative yields under mild conditions and without the use of oxidizing agents.

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**Supplementary Material Available:** Experimental details and spectroscopic data for all compounds (3 pages).

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