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## A PREPARATIVE SCALE REDUCTION OF ALKYL DISULFIDES WITH TRIBUTYL PHOSPHINE AND WATER

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A series of alkyl disulfides has been shown to be reduced by tributyl phosphine at room temperature. The resulting thiols were then acylated in the same pot and isolated in good yields. This sequence is convenient and is a practical option for the preparation of gram quantities of thiol or thioester from the corresponding disulfide.

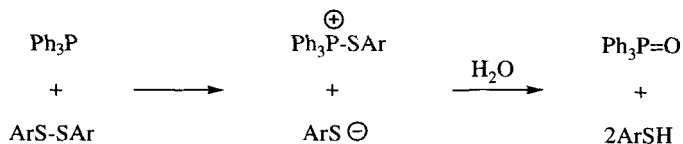
The transformation of disulfides to thiols or thioesters is an important process both in synthetic organic chemistry and biochemistry. Because of its broad application, many approaches have been reported for reducing disulfides. Some of the more common reducing agents include sodium borohydride,<sup>1</sup> lithium aluminum hydride<sup>2</sup>, potassium triisopropoxy borohydride (KIPBH)<sup>3</sup>, lithium tris(dialkylamino)aluminum hydrides<sup>4</sup>, zinc with dilute acid<sup>5</sup>, lithium tri-*tert*-butoxyaluminum hydride<sup>6</sup>, triphenyl phosphine<sup>7</sup>, and tributyl phosphine<sup>8</sup>. The reagent of choice will often differ depending on the system of interest.

Phosphine reagents are particularly appealing in many circumstances due to their broad functional group tolerance, mild conditions, and high yields. Aryl disulfides have been shown to be readily reduced to their corresponding thiols by

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triphenyl phosphine at room temperature.<sup>7</sup> Dialkyl disulfides, however, are either partially reduced or not reduced under these conditions, even with prolonged reaction periods and elevated temperatures.<sup>7f,7g,8a</sup> The mechanism of reduction by triphenyl phosphine has been studied extensively.<sup>7</sup> Due to the fact that one equivalent of water is consumed during the course of the reaction, reductions with triphenyl phosphine typically are carried out in a mixed solvent containing an aqueous portion. Various systems have been reported: methanol/ water (1:9), dioxane/water (1:1), and THF/water (12:1).<sup>7</sup>



Tributyl phosphine has been shown to reduce dialkyl disulfides, but it has seen limited use as a preparative reagent.<sup>8</sup> Here we describe the use of tributyl phosphine as a preparative reagent in the production of thioesters from the corresponding disulfides using a two-step, one-pot reduction/acylation sequence. As we are interested in synthesizing a series of thioesters for biological binding studies, this procedure proved quite practical. It allowed us to avoid isolating the intermediate thiol, thereby decreasing the chance that the thiol would reoxidize to the disulfide and minimizing the unpleasant odor associated with low molecular weight thiols.



In an effort to optimize the conditions for a one-pot reduction/acylation reaction, we decided to explore various solvent systems. Typical solvents systems for

tributyl phosphine include methanol/water (1:9) and THF/water (20:1).<sup>8</sup> We had encountered solubility problems using THF and water. Moreover, if possible, we wanted to use a non-nucleophilic solvent with a stoichiometric amount of water so that we could carry the thiol directly into the acylation step without workup. We selected the reduction of dibutyl disulfide as our model system and considered a range of solvents. As can be seen in Table 1, the solvent had a rather large effect on the rate of reduction of the dibutyl disulfide. The less polar solvents showed a much slower rate of reduction than the more polar solvents, and only pyridine and DMF resulted in complete reduction of the dibutyl disulfide within the observed time period.<sup>9</sup> Although THF is the most commonly used solvent in the literature, the more polar solvents were favorable.

**Table 1.** Reduction of Dibutyl Disulfide with Tributyl Phosphine

Solvent	Reduction Time (hr)	Percent Reduction <sup>a</sup>
Ether	1	17%
Toluene	1	20%
THF	1	56%
Pyridine	0.5	>95%
DMF	0.5	>95%

<sup>a</sup> NMR ratios

In order to ascertain the generality of the one-pot reduction/acylation reaction, we considered a series of disulfides (Table 2). In all cases, the rate of reduction was comparable or faster in pyridine/DMF than in THF. Both aryl and alkyl disulfides could be essentially quantitatively reduced in one hour or less, with the exception of the di-*sec*-butyl disulfide.<sup>10</sup> Overall yields for the corresponding thioesters ranged from 49 to >95%.<sup>11</sup>

**Table 2.** Reduction and Acylation of Alkyl Disulfides by Tributyl Phosphine

Disulfide	Solvent	Reduction Time (hr)	Percent Reduction <sup>a</sup>	% Yield of Thioester <sup>b</sup>
Diphenyl <sup>c</sup>	THF	0.5	>95%	97%
	pyridine	0.5	>95%	96%
	DMF	0.5	>95%	90%
Dibenzyl	THF	0.5	85% <sup>d</sup>	-
	pyridine	0.5	>95%	99%
	DMF	0.5	>95%	97%
Dibutyl	THF	0.5	53% <sup>d</sup>	-
	pyridine	0.5	>95%	61% <sup>e</sup>
	DMF	0.5	>95%	63% <sup>e</sup>
Di- <i>sec</i> -Butyl	THF	1	5% <sup>d</sup>	-
	THF	3	8%	-
	pyridine	1	33%	-
	pyridine	3	52%	-
	DMF	0.5	66%	-
	DMF	3	82%	49% <sup>e</sup>
Furfuryl (C <sub>10</sub> H <sub>10</sub> O <sub>2</sub> S <sub>2</sub> )	THF	0.5	>95%	90%
	pyridine	0.5	>95%	95%
	DMF	0.5	95%	73%

<sup>a</sup> NMR ratios <sup>b</sup> Isolated yields <sup>c</sup> Used for comparison with previously reported triphenyl phosphine data. <sup>d</sup> Reactions that showed incomplete reduction were not purified further. <sup>e</sup> Reduced yields due to incomplete reduction and/or the volatility of the low molecular weight thiols and thioesters.

## EXPERIMENTAL

**General.** <sup>1</sup>H NMR spectra were obtained on a General Electric QE-300 instrument at 300 MHz. Spectra were recorded in CDCl<sub>3</sub>. Chemical shifts are reported in ppm (δ) relative to a TMS standard. Mass spectra were obtained on a Hewlett-Packard Model GCD gas chromatograph/mass spectrometer with a HP-5 column (crosslinked 5% PH NE silicone, 30 m x 0.32 mm). All spectra were

obtained at an ionization potential of 70 eV and are reported as  $m/z$  (intensity relative to base peak of 100). GC purities were obtained on a Hewlett-Packard Model 5890 gas chromatograph with a HP-5 column (crosslinked 5% PH NE silicone, 30 m x 0.32 mm) and an FID detector.

Phenyl disulfide, benzyl disulfide, butyl disulfide, sec-butyl disulfide, furfuryl disulfide, tributyl phosphine, acetic anhydride, acetyl chloride, and triethylamine were purchased from Acros, Aldrich, or Sigma chemicals. All solvents were reagent grade.

**Typical Procedure for the Preparation of the Thioesters.** Disulfide (4.6 mmol) and water (84 mL, 4.7 mmol) were dissolved in 25 mL of DMF in a 100 mL round bottom flask. The flask was flushed thoroughly with  $N_2$ , and tributyl phosphine (1.7 mL, 6.8 mmol) was added. The solution was stirred for 1 hr at room temperature, acetic anhydride<sup>12</sup> (1.3 mL, 13.8 mmol) was added, and the reaction was stirred for an additional hour. The reaction mixture was diluted with 50 mL of ethyl acetate, washed with 1M HCl (3 x 30 mL), dried over sodium sulfate, and concentrated in vacuo to yield an oily residue. The resulting products were subsequently purified by flash chromatography (1-5% ethyl acetate in hexanes).

**Phenyl Thioacetate.** Purification yielded a clear oil in 94% overall yield.  $^1H$ -NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.41 (s, 3H), 7.41 (s, 5H). GC-MS  $m/z$  152 (10), 110 (100). GC purity (60°C - 250°C at 20°C/min) -  $t_R$  7.56 min, 98.7%.

**Benzyl Thioacetate.** Purification yielded a clear oil in 97% overall yield.  $^1H$ -NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.33 (s, 3H), 4.13 (s, 2H), 7.30 (bs, 5H). GC-MS  $m/z$  166 (20), 123 (23), 91 (100). GC purity (60°C - 250°C at 20°C/min) -  $t_R$  8.40 min, 94.4%.

**Butyl Thioacetate.** Purification yielded a clear oil in 63% overall yield.  $^1H$ -NMR ( $CDCl_3$ , 300 MHz)  $\delta$  0.91 (t, 3H,  $J = 7.19$  Hz), 1.39 (m, 2H), 1.55 (m,

2H), 2.32 (s, 3H), 2.87 (t, 2H,  $J = 7.11$  Hz). GC-MS  $m/z$  132 (32), 77 (49), 72 (58), 56 (100), 47 (30). GC purity (60°C - 250°C at 20°C/min) -  $t_R$  4.87 min, 98.9%.

**sec-Butyl Thioacetate.** Purification yielded a clear oil in 49% overall yield.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.95 (t, 3H,  $J = 7.34$  Hz), 1.38 (d, 3H,  $J = 7.07$  Hz), 1.65 (m, 2H), 2.25 (s, 3H), 3.50 (m, 1H). GC-MS  $m/z$  132 (77), 89 (22), 77 (93), 61 (57), 56 (100). GC purity (60°C - 250°C at 20°C/min) -  $t_R$  4.29 min, 94.6%.

**Furfuryl Thioacetate.** Purification yielded a clear oil in 95% overall yield.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.36 (s, 3H), 4.15 (s, 2H), 6.22 (d, 1H,  $J = 3.18$  Hz), 6.29 (d, 1H,  $J = 3.18$  Hz), 7.35 (s, 1H). GC-MS  $m/z$  156 (16), 81 (100), 53 (18). GC purity (60°C - 250°C at 20°C/min) -  $t_R$  6.84 min, 94.0%.

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- 9 The fact that the reductions were more rapid in pyridine raised the question as to whether pyridine may be acting as a sulfur transfer reagent. To test this possibility, one to five equivalents of pyridine or DMAP were added to the reaction in THF. The rate of reduction was not enhanced by the presence of these potential transfer catalysts.
- 10 The extent of reduction was determined by comparing the NMR ratios of unreacted disulfide to the thioester product.
- 11 Yields for the smaller, more volatile, butyl thiols/thioesters were significantly lower than those for the diphenyl and dibenzyl thioesters. This most likely reflects losses due to the evaporation of the volatile thiol intermediates and thioester products.

- <sup>12</sup> Acetyl chloride was also used but resulted in overall yields that were slightly lower.

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