Selective Reduction of Disulfides to Thiols with Potassium Triisopropoxyborohydride

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Potassium triisopropoxyborohydride (**2**; KIPBH)[2,3] is a mild reducing agent which readily reduces only the carbonyl group of aldehydes and ketones among the wide variety of functional groups examined[4,5]. We now report that it readily reduces both aliphatic and aromatic disulfides to the coresponding thiols. Moreover, it selectively reduces aromatic disulfides in the presence of aliphatic disulfides. Consequently, it is now possible to reduce selectively disulfides in the presence of most other functional groups.

The sulfur-sulfur bond in disulfides plays an important role in biological activity. Hence, the conversion of the sulfur-sulfur bond in disulfides to thiols has been subjected to considerable study[6]. This conversion can be achieved most easily by reduction[7]. The reagents utilized include lithium aluminum hydride[8], sodium borohydride[9], sodium borohydride/aluminum chloride[10], zinc/acetic acid[11], triphenylphosphine[12], as well as other miscellaneous reagents[13].

Of the various reagents available, lithium aluminum hydride[8c] and sodium borohydride/aluminum chloride[10a] are strong reducing agents capable of attacking practically all functional groups with little discrimination. Unfortunately, sodium borohydride, a mild reducing agent[9], possesses little solubility in convenient organic solvents (diethyl ether, tetrahydrofuran, monoglyme). Other reduction methods, based on tin, zinc or zinc/mercury in the presence of an acid, suffer from the disadvantage of being heterogeneous systems[11]. Potassium triisopropoxyborohydride (**2**), however, is a mild reducing agent[4a] and is readily soluble in desirable organic solvents (diethyl ether, tetrahydrofuran, monoglyme). Accordingly, when a detailed survey of the reducing properties of **2**[4b] revealed that this reagent readily reduces disulfides to thiols and gives somewhat higher yields than the corresponding reductions based on triphenylphosphine and water[12] (Table 1), we undertook a detailed study of the reaction.

The initial reaction (0 °C or 25 °C) proceeds with the uptake of one hydride per mole of disulfide **1**, forming equimolar amounts of the product **4** and its potassium salt **3**. Treatment of the product with acid liberates the thiol **4** in essentially quantitative yield (Reactions *1* and *2*).

(1) $\underset{\mathbf{1}}{R{-}S{-}S{-}R} + \underset{\mathbf{2}}{KBH(OC_3H_7\text{-}i)_3} \longrightarrow \underset{\mathbf{3}}{R{-}SK} + \underset{\mathbf{4}}{R{-}SH} + \underset{\mathbf{5}}{B(OC_3H_7\text{-}i)_3}$

(2) $\underset{\mathbf{3}}{R{-}SK} + HX \longrightarrow \underset{\mathbf{4}}{R{-}SH} + KX$

Simple distillation, in the case of volatile products, or crystallization, in the case of solid products, provides the thiols in essentially quantitative yields.

There is a slow subsequent evolution of hydrogen produced in the slow reaction of thiol **4** with excess reagent **2** (Reaction *3*). However, this does not affect the yield.

(3) $\underset{\mathbf{4}}{R{-}SH} + \underset{\mathbf{2}}{KBH(OC_3H_7\text{-}i)_3} \longrightarrow \underset{\mathbf{5}}{R{-}SK} + H_2 + B(OC_3H_7\text{-}i)_3$

The reduction of aromatic disulfide is much faster than aliphatic. Consequently, the former reduction is conveniently carried out at 0 °C (15 min), whereas, it is convenient to carry out the latter at 25 °C (5 h). These results for representative reductions are summarized in Table 1.

The remarkable difference in the rate of reduction of aromatic and aliphatic disulfides has also been observed with aluminum hydride[14], lithium tri-*t*-butoxyaluminum hydride[15] and triphenylphosphine[12c]. However, since **2** is such a mild reducing agent[4], it was of interest to test the practicality of a

Table 1. Reduction of Disulfides with Potassium Triisopropoxyborohydride (**2**) in Tetrahydrofuran[a]

Compound	Temp. [°C]	Time [h]	Product	Yield[b] [%]	m.p. [°C] or b.p. [°C]/torr	Literature Data[17]
bis[*o*-nitrophenyl] disulfide	0°	0.25	*o*-nitrothiophenol	92(81)[c]	58°	58.5°
bis[*p*-chlorophenyl] disulfide	0°	0.25	*p*-chlorothiophenol	90	53–54°	54°
diphenyl disulfide	0°	0.25	thiophenol	83(69)[c]	169°/760	168.7°/760
di-*n*-butyl disulfide	25°	5	1-butanethiol	81	97–98°/760	98.46°/760
dibenzyl disulfide	25°	5	benzyl thiol	84	193–195°/760	194–195°

[a] Disulfide concentration ≈0.7 molar, reagent **2** concentration ≈1.4 molar.

[b] All products are isolated by distillation or recrystallization and the purity of products is confirmed by ^{1}H-N.M.R., G.L.C., m.p. and refractive index.

[c] Using $(C_6H_5)_3P$ and water, *m*-nitrothiophenol and thiophenol were obtained in 81% and 69% yields, respectively: Ref.[12c].

procedure under preparative conditions for the selective reduction of aromatic disulfides in the presence of an aliphatic disulfide. Indeed, we achieved up to 99% reduction of diphenyl disulfide, with only minor reduction of di-*n*-butyl disulfide (Table 2).

Table 2. Selective Reduction of Diphenyl Disulfide in the Presence of Di-*n*-butyl Disulfide with Potassium Triisopropoxyborohydride in Tetrahydrofuran at 0°C[a]

Ratio of Disulfide:	Time	Mol [%] of Product[b]	
Reagent **2**	[h]	Thiophenol	1-Butanethiol
1:1.0	1.0	69	2
1:1.1	1.0	73	2
1:1.5	0.5	95	2.5
1:2.0	0.25	99	7

[a] The reaction mixture was 0.25 molar in each of the disulfides.
[b] Determined by G.L.C. from the response ratios determined by authentic samples.

Finally, another significant application may be pointed out. An oxidation of thiols storage is a frequent problem. Indeed, storage of the thiols as disulfides has been recommended[16]. Consequently, the thiol could be stored as a stable disulfide and the thiol regenerated as needed by application of reagent **2**.

Reduction of Bis[*o*-nitrophenyl] Disulfide with Potassium Triisopropoxyborohydride (2):

To a 100-ml, oven-dried, round-bottom flask fitted with a sidearm and capped with a rubber septum is added bis [*o*-nitrophenyl] disulfide (6.16 g, 20 mmol) under nitrogen. To this is added freshly distilled tetrahydrofuran (10 ml) to make a yellow-colored slurry of the disulfide in the solvent. The flask is immersed in an ice/water bath. To the reaction mixture is slowly added a 2.1 molar solution of **2** in tetrahydrofuran (19 ml)[3]. The color of the mixture turns to red-brown immediately after the addition of the hydride reagent and the mixture becomes homogeneous. Partial hydrogen formation is observed during this period. After 15 min, the reaction is quenched with water (2 ml) and acidified with 15% sulfuric acid. The product is then extracted with diethyl ether (3 × 50 ml). The organic layer is washed with a saturated solution of sodium chloride and dried with anhydrous magnesium sulfate. The ether is then evaporated to give the desired thiol compound, *o*-nitrophenyl thiol, in quantitative yield. The crude product is recrystallized from hot water to give the pure product; yield: 5.70 g (92%); m.p. 58°C (Lit.[17], m.p. 58.5°C).

Reduction of Dibenzyl Disulfide with Potassium Triisopropoxyborohydride (2):

To a 250-ml, oven-dried, round-bottom flask fitted with a sidearm and capped with a rubber septum is added dibenzyl disulfide (6.16 g, 25 mmol) under nitrogen. To this is then added tetrahydrofuran (12 ml). The mixture is kept at room temperature by using a water-bath. To the mixture is then added a 2.1 molar solution of **2** in tetrahydrofuran (23.8 ml)[3]. The mixture is stirred at room temperature for 5 h. During this time, a white precipitate forms. The mixture is quenched water (5 ml) and acidified with 15% sulfuric acid. Extraction with ether, followed by distillation at atmospheric pressure, results in pure benzyl thiol; yield: 5.21 g (84%); b.p. 193–195°C; n_D^{20}: 1.5752 (Lit.[17], b.p. 194–195°C; n_D^{20}: 1.5751). The purity is confirmed by G.L.C. analysis (≥ 99.9%).

Selective Reduction of Diphenyl Disulfide in the Presence of Di-*n*-butyl Disulfide with Reagent 2 (1:1.5):

A 100-ml, round-bottom flask with a sidearm is charged with tetrahydrofuran (4.6 ml) and tetrahydrofuran solution of diphenyl disulfide and di-*n*-butyl disulfide (1.0 molar in each; 2 mmol of each disulfide) containing *n*-octane as an internal standard. The mixture is kept at 0°C with an ice/water bath. To this is then added a 2.1 molar solution of **2** in tetrahydrofuran (1.43 ml). The white precipitate forms immediately. After stirring for 0.5 h, the reaction is quenched with water (1 ml) and acidified with 15% sulfuric acid. G.L.C. analysis of the organic layer indicates a 95% yield of thiophenol and a 2.5% yield of 1-butanethiol.

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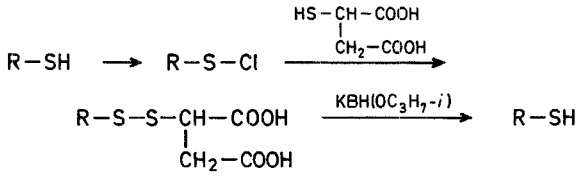

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