Reductions using LiCl/NaBH₄: A rapid and efficient cleavage of organic disulfides to mercaptans†

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A practical and novel reagent system LiCl/NaBH₄ is used for the reductive cleavage of organic disulfides to mercaptans under mild conditions, in excellent yields.

The universal presence of disulfide and thio moieties in biologically active compounds has led to many new and varied methods for their interconversion¹². Some of the reported methods include sodium hydrogen telluride³, meso-2, 5-dithiol-N, N', N'-tetramethyldapiamide (meso-DTA)⁴, potassium triisopropoxy borohydride (KIPBH)⁵, Zn or Sn in the presence of an acid⁶, Ph₃P-dioxane-water⁷, In-NH₄Cl⁸. However, these methods suffer from drawbacks such as prolonged reaction period, higher reaction temperature⁹, and ineffectiveness towards stearically hindered disulfides⁹⁰.

Sodium borohydride is considered to be a very mild reducing agent. Methods previously used to modify NaBH₄ reactivity include the use of solvent effects and exchange of sodium with other metal cations in the complex hydride¹¹. In continuation of our efforts towards modified borohydride reagents¹²,¹³ for organic transformations, we observed that a combination of NaBH₄ and LiCl could bring about the efficient conversion of organic disulfides to corresponding mercaptans. In this note we report the potential utility of LiCl/NaBH₄ reagent system for the reductive cleavage of organic disulfides within 30 min under mild reaction conditions to give high yields of the corresponding mercaptans.

Treatment of one equivalent of an organic disulfide with one equivalent of LiCl/NaBH₄ reagent system in dry THF under nitrogen at 0°C to room temperature provided quantitative formation of the corresponding mercaptans (Scheme I).

When LiCl (1 eq.) reacts with NaBH₄ (1 eq.), this generates in situ formation of LiBH₄¹¹. The formation of mercaptans from corresponding organic disulfides is probably due to the in situ formation of LiBH₄. The formation of mercaptans from the organic disulfides can be visualized as an initial conjugation of Lithium with the disulfide leading to the formation of the sulfonium ion followed by the hydride delivery (Scheme II).

The generality of the reaction to various disulfides is shown in Table I. Both aliphatic and aromatic including heteroaromatic disulfides are converted smoothly to the mercapto compounds within 30 min. Chemoselective reduction of disulfides is observed in the presence of chloro (entry 4), and nitro (entry 6).

![Scheme I](image_url)

![Scheme II](image_url)

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### Table I—Reduction of disulfides to mercaptans using LiCl/NaBH₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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</table>

*a* all the reactions were completed in 20-30 min.

*b* isolated yields by silica gel column chromatography (yields unoptimized)

*c* observed difficulty in isolation due to low b.p. (98 °C)
groups. All the products thus obtained were fully characterized by $^1$H NMR, IR and mass fragmentation analysis.

In conclusion, we have developed an efficient and rapid methodology for the reductive cleavage of a wide range of disulfides to their respective mercaptans in excellent yields under mild reaction conditions using LiCl/NaBH$_4$.

Experimental Section

Typical procedure. Into a two-necked round bottom flask equipped with magnetic bead and nitrogen balloon adaptor was placed LiCl (1 eq.) and dry THF (5 mL) syringed into it. The contents were cooled to 0°C, and NaBH$_4$ (1 eq.) was added in portions. To this reagent system at 0°C was added disulfide (1 eq.) in dry THF (5 mL) and the contents stirred magnetically. After the addition of disulfide, ice cooling was removed and the contents brought to room temperature (35°C). The progress of the reaction monitored by TLC clearly indicated the disappearance of the disulfide in 15 min. The contents were cooled and treated with 5% aq. HCl. The organic layer thus separated was evaporated under vacuum to remove THF. It was extracted with ethyl acetate (10 mL), washed with water and dried over anhydrous Na$_2$SO$_4$. Evaporation of the organic portion followed by silica gel column chromatography provided pure thiol in quantitative yield.

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References and Notes