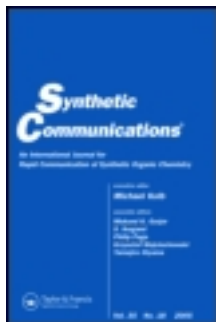


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A RAPID AND EFFICIENT CLEAVAGE OF ORGANIC DISULFIDES TO MERCAPTANS USING $ZrCl_4/NaBH_4$

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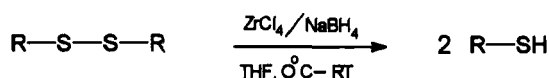
Abstract: A practical & cheaper reagent system $ZrCl_4/NaBH_4$ is used for the reductive cleavage of organic disulfides to mercaptans under mild conditions, in excellent yields.

The ubiquitous presence of disulfide and thio moieties in biologically active compounds such as biotin and its biosynthetic intermediates, peptides and ribosides has led to many new and varied methods for their inter conversion.^{1,2} A host of reagents were reported for the conversion of disulfides to the corresponding mercaptans. They include glucose in basic ethanol solution,³ sodium sulfide, hypophosphorous acid in the presence of catalytic diselenide,⁴ sodium hydrogen telluride,⁵ meso-2, 5-dithiol-N,N,N',N'-tetramethyl adipamide (meso-DTA),⁶ potassium triisopropoxy borohydride (KIPBH),⁷ Zn or Sn in the presence of an acid,⁸ metal amalgams,⁹ Na/liquid ammonia,¹⁰ tributyl phosphine,¹¹ Ph_3P -dioxane-water,¹² $TiCl_3$,¹³ Mg in methanol¹⁴ and $In-NH_4Cl$.¹⁵ However, the methods suffer from some drawbacks such as prolonged reaction time, higher

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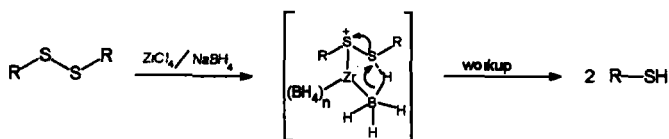
reaction temperature,⁵ and ineffectiveness towards sterically hindered disulfides¹⁶ etc. In the course of our program to explore the novel utilities of $ZrCl_4/NaBH_4$ reagent system¹⁷⁻¹⁹ we observed that this reagent system effectively furnishes mercaptans from their respective organic disulfides within thirty minutes at room temperature under mild reaction conditions. $ZrCl_4/NaBH_4$ reagent system is found to be much superior in comparison with In/NH_4Cl ,¹⁵ that we disclosed recently for this transformation. In/NH_4Cl reagent system requires reflux reaction conditions in ethanol solvent for the conversion of disulfides to thiols. In this communication we disclose the potentiality of $ZrCl_4/NaBH_4$ for an efficient cleavage of disulfides to furnish corresponding mercaptans.

Treatment of one equivalent of organic disulfide with one equivalent of $ZrCl_4/NaBH_4$ reagent system in dry THF solvent under nitrogen balloon atmosphere at 0 °C to room temperature provided quantitative formation of the mercaptans²⁰ (Scheme 1).



Scheme 1

The formation of mercaptans from the organic disulfides can be visualized as an initial conjugation of zirconium with the disulfide leading to the formation of the sulfonium ion followed by the hydride delivery (Scheme 2).



Scheme 2

Table

Entry	Substrate	Product	Time (min)	Yield (%)
1			10	90
2			10	90
3			15	80
4			20	90
5			15	95
6			15	95
7			10	85
8			15	85
9			10	90
10			10	90
11			10	95
12			10	80:20
			30	10:90
13			10	80:20
			30	10:90
14			20	80
15			10	95

The generality of the reaction to various organic disulfides is shown in the **Table**. Both aliphatic and aromatic including heteroaromatic disulfides are converted smoothly to the mercapto compounds within thirty minutes. Chloro substituent is unaffected during the reaction. However, the nitro disulfides (**entry 12 and 13**) showed time dependent selectivity in the reaction. Chemospecific cleavage of the nitro disulfide (**entry 13**) was achieved by controlling the reaction time. Shorter reaction time i.e., in less than ten minutes gave predominantly 2-nitro mercaptan^{21a} (2-nitro mercaptan:2-amino mercaptan, 8:2), while increased reaction time (~30 minutes) resulted in reduction of nitro functionality furnishing 2-amino mercaptan^{21b} (2-nitro mercaptan:2-amino mercaptan, 1:9) as a major product which is a key precursor of 2, 3 dihydro-1, 5 benzothiazepin-4 (5H)-ones for the studies of CNS activity.²² As a representative of aliphatic disulfides, diethyl disulfide (**entry 15**) was treated with this reagent system. To our surprise, progress of the reaction monitored by TLC clearly indicated the disappearance of the disulfide within ten minutes. Since it is difficult to isolate the product (ethane thiol, b.p = 35 °C), and based on the disappearance of the diethyl disulfide (monitored by TLC), we quantified the conversion as 95%. All the products thus obtained were fully characterized by H¹ NMR, IR and Mass fragmentation spectral analysis and compared with their spectral data known in the literature.

In summary, we have developed an efficient and rapid methodology for the reductive cleavage of a wide range of organic disulfides to their respective mercaptans in excellent yields under mild reaction conditions using ZrCl₄/NaBH₄.

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20. **Typical Experimental Procedure:** Into a two necked round bottom flask equipped with magnetic bead and nitrogen balloon adopter was placed $ZrCl_4$ (0.189g, 0.81mmol), dry THF (5 ml) was syringed into the flask. Immediate formation of reddish brown solution was observed. The contents were cooled to 0 °C, $NaBH_4$ (0.123g, 3.246 mmol) was added in portion to the above solution. Reddish brown solution slowly turned to pale pink. To this reagent system at 0 °C was added p-tolyl disulfide (entry 5)(0.2g, 0.8 mmol) in dry THF (5 ml). Contents were stirred magnetically. After completion of addition of disulfide ice cooling was removed and contents were brought to room temperature (35 °C). The progress of the reaction monitored by TLC clearly indicated the disappearance of the disulfide in 15 minutes. Contents were cooled and treated with 20% aq. HCl solution gave the separation of organic layer. THF was evaporated under vacuum, extracted into ethyl acetate (10 ml), washed with water and dried over anhydrous Na_2SO_4 . Evaporation of the organic portion followed by silicagel column chromatography provided pure 4-methylbenzene thiol (0.191g, 95% yield), a low melting solid.
21. **H^1 NMR analysis data of time dependent chemoselective cleavage of Nitro Disulfides to Mercaptans:**
- a) Entry 13 [Analysis of the crude reaction mixture, after workup in 10 minutes] :** (200 MHz H^1 NMR, δ ppm, in $CDCl_3$)
[δ 3.2 (br, SH), 7.03 (m, 1H, ortho hydrogen w.r.to SH), 7.2-7.3 (m, 2H, aromatic hydrogens), 8.24 (m, 1H, ortho hydrogen w.r.to NO_2) & 6.68-7.0 (m, 1H, ortho hydrogen w.r.to SH)] measurement of integration indicated a ratio of 2-Nitro-1-benzenethiol : 2-amino-1-benzenethiol as 80:20. Later the mixture was subjected to silicagel column chromatography purification, provided pure 2-Nitro-1-benzenethiol (low melting solid, m.p 58 °C, isolated yield 80%) and 2-amino-1-benzenethiol (liquid, isolated yield 20%).
- b) Entry 13 [Analysis of crude reaction mixture, after workup in 30 minutes] :** (200 MHz H^1 NMR, δ ppm, in $CDCl_3$)
[δ 3.2 (br, SH), 6.6-6.7 (m, 1H, ortho hydrogen w.r.to SH), 6.8-7.0 (m, 1H, ortho hydrogen w.r.to NH_2) 7.0-7.1 (m, 2H, aromatic) & 8.2 (m, 1H, ortho hydrogen w.r.to NO_2)] measurement of integration indicated a ratio of 2-Nitro-1-benzenethiol : 2-amino-1-benzenethiol as 10:90. Later the mixture was subjected to silicagel column chromatography purification, provided pure

2-Nitro-1-benzenethiol (low melting solid, m.p 58 °C, isolated yield 10%) and 2-amino-1-benzenethiol (liquid, isolated yield 90%).

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