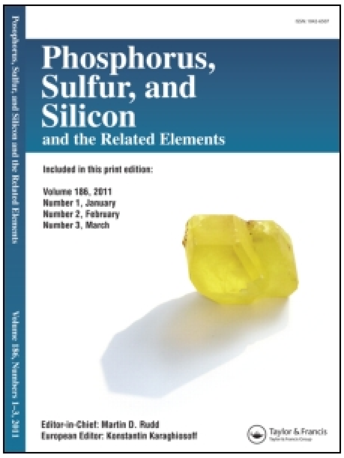

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EFFICIENT REDUCTION OF ORGANIC COMPOUNDS WITH SULFURATED CALCIUM BOROHYDRIDE [$Ca(S_3BH_2)_2$], A NEW AND STABLE MODIFIED BOROHYDRIDE REAGENT

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EFFICIENT REDUCTION OF ORGANIC COMPOUNDS WITH SULFURATED CALCIUM BOROHYDRIDE [$Ca(S_3BH_2)_2$], A NEW AND STABLE MODIFIED BOROHYDRIDE REAGENT

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Sulfurated Calcium, magnesium, and berelium borohydrides are prepared by metathetical reaction between $NaBH_2S_3$ and Ca, Mg, and Be chlorides in dry THF and the effect of metal cation exchange on their stability and reactivity has been presented. In this study we have shown that $Ca(BH_2S_3)_2$ is much more stable and more reactive than its Mg, Be, and Na analogues. $Ca(BH_2S_3)_2$can easily reduce carbonyl compounds such as aldehydes, ketones, acyloins, α-diketones, α-β-unsaturated carbonyl compounds, aroyl azides, and carboxylic acid chlorides to their corresponding alcohols in good to excellent yields. Epoxides are also effected by this reagent and produce their symmetrical dihydroxydisulfides in good yields.

Keywords: Reduction; Sulfurated Sodium; Beryllium; Magnesium; and Calcium Borohydrides; Epoxides; Alcohols; Carbonyl Compounds; Dihydroxydisulfides; THF

INTRODUCTION

Sodium borohydride is a mild reducing agent and is usually used for the reduction of aldehydes and ketones in protic solvents[1]. In spite of easy application of $NaBH_4$, limitations are observed by using this reagent, which could by summarized as: essential need of polar and protic solvents, limited number of functional groups are reduced, rate of the reductions is sometimes slow and low selectivity is accompanied with the reactions[1,2].

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* Correspondence author.

In order to affect the reactivity of $NaBH_4$, structural modifications have been made upon the reagent and various modified borohydrides are reported in the literature. The preparation and application of modified borohydrides in organic synthesis have been reviewed recently[3]. The modifications may be summarized as the substitutions of one or more hydrides with other substituents[4,5], exchange of the metal cation with other metal cations[6,7], a concurrent cation and hydride exchange[8,9], ligand-metal borohydrides[10], combination of hydride transfer agents with metals, metal salts, Lewis acids[11], solid supports[12] and by the exchange of quaternary ammonium[13,14] or phosphonium[15] cations with the metal cations of the hydride transfer agents.

Treatment of $NaBH_4$ with a controlled amount of sulfur in anhydrous THF under nitrogen atmosphere produces sodium sulfurated borohydride, $NaBH_2S_3$accompanied with the evolution of hydrogen gas[16]. This compound is produced by the substitution of two hydride ions with the $S_3^=$ moiety. This exchange affects dramatically the reactivity and versatility of the reagent in comparison with its parent compound, $NaBH_4$. There are extensive reports available in the literature on the use of this compound as reducing agent[16]. The instability of the reagent which decomposes rapidly in the presence of oxygen or atmospheric moisture puts limitations on its uses as a practical reducing agent. Search in the literature revealed that there is no report on the preparation and uses of the modified form of this reagent in order to decrease or overcome its drawbacks.

In continuation of our interest for the preparation of new modified borohydrides[13–15], we now wish to report the preparation of sulfurated beryllium, magnesium, and calcium borohydrides; $Be(BH_2S_3)_2$, $Mg(BH_2S_3)_2$ and $Ca(BH_2S_3)_2$ and the study of the effect of the metal cation exchange upon the stability and their reactivity in reduction of organic compounds in comparison with $NaBH_2S_3$.

RESULTS AND DISCUSSION

$NaBH_2S_3$ was prepared by mixing $NaBH_4$ and sulfur in THF according to eq. 1.

$$NaBH_4 + 3S \longrightarrow NaBH_2S_3 + H_2 \quad \text{(eq 1)}$$

$NaBH_2S_3$ was prepared in our laboratories and was subsequently used for the preparation of $Be(BH_2S_3)_2$, $Mg(BH_2S_3)_2$ and $Ca(BH_2S_3)_2$, by metathetical reactions with $BeCl_2$, $MgCl_2$ and $CaCl_2$ in dry THF under an inert atmosphere at room temperature (eq 2).

$$2NaBH_2S_3 + MCl_2 \longrightarrow M(BH_2S_3)_2 + 2NaCl \quad \text{(eq 2)}$$
$$M = Mg^{+2}, Be^{+2}, Ca^{+2}$$

The effect of metal cation exchange on the stability of sulfurated borohydride has been shown by the acidic hydrolysis of the borohydrides and is demonstrated by plotting the amount of hydrogen evolved during the hydrolytic reaction versus different time intervals for portions of 0.1 g of the compounds. The comparisons of the results show that the order of the stabilities of the new sulfurated borohydrides is: $Ca^{+2}>Be^{+2}>Na^{+}>Mg^{+2}$. Therefore, during this study we have paid attention to $Ca(BH_2S_3)_2$ which is the most stable compound in this series. The yield of the formation of $Ca(BH_2S_3)_2$ is almost quantitative. The color of the reagent is faint yellow; it decomposes above 242°C. This reagent is insoluble and stable in solvents such as acetone, CCl_4, THF, CH_2ClCH_2Cl, benzene and toluene. $Ca(BH_2S_3)_2$ reacts vigorously with DMSO, DMF, HMPA and H_2O but reacts slowly with CH_3OH.

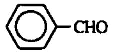
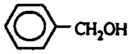
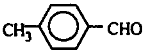
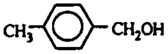
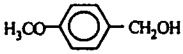
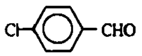
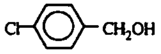
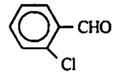
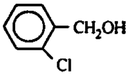
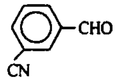
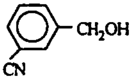
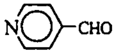
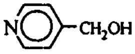
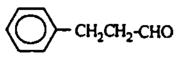
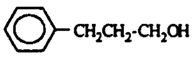
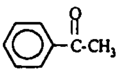
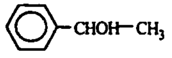
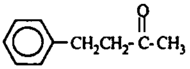
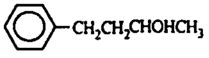
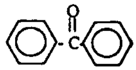
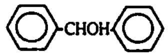
Very recently, we have reported the efficient reduction of aryl azides and aryl nitro compounds with $Ca(BH_2S_3)_2$ in dry THF to their corresponding amines with high yilds.[17] In this paper we describe the other applications of this new modified borohydride agent for the reductive conversion of other functional groups.

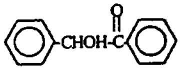
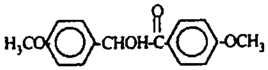
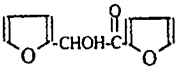
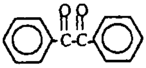
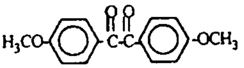
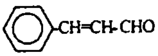
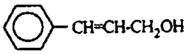
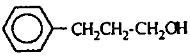
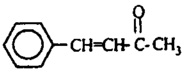
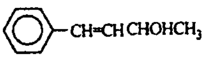
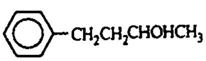
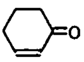
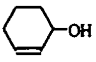
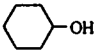
1. Reduction of Carbonyl Compounds

$NaBH_4$ is usually used for the reduction of aldehydes and ketones to their corresponding alcohols in protic solvents. $Ca(BH_2S_3)_2$ effects reductive conversion of aldehydes and ketones easily in high yields (83–91%) in THF under reflux conditions. α-Hydroxyketones and α-diketones were reduced to their corresponding α-dihydroxy compounds in good yields (76–81%) in dry THF under reflux cnditions. α,β- Unsaturated carbonyl compounds were also reduced by $Ca(BH_2S_3)_2$ under the same reaction conditions. The reagent shows good regioselectivity and 1,2 versus 1,4 reductions were observed with the ratios of 4–7.3. Chemoselectivity among different carbonyl groups has not been observed with this reagent.

α,β-Unsaturated carbonyl compounds were reduced mostly by a 1,2-reduction to produce the corresponding allyl alcohols (entries 16–21, Table I). The results are tabulated in Table I.

TABLE I Reduction of Aldehydes, Ketones, Acyloins, α- Diketones and α-β Unsaturated Carbonyl Compounds with $Ca(BH_2S_3)_2$ in Dry THF. [a,b,c]

Entry	*Substrate*	*Product*	*Time (h)*	*Yield %*
1			0.8	83
2			1	88
3			1.8	83
4			1.5	91
5			2	84
6			1.2	93
7			1.2	86
8			1.4	88
9	$(CH_3)_2C=CH-(CH_2)_3-CHO$	$(CH_3)_2C=CH-(CH_2)_3-CH_2OH$	3	80
10			1.5	89
11			2	87
12			5.5	90

Entry	*Substrate*	*Product*	*Time (h)*	*Yield %*
13			2.5	81
14			4.5	80
15			3	76
16			4.5	79
17			7.5	76
18			1.3	70
				14
19	CH_3-$(CH_2)_3$-CH=CH-CHO	CH_3-$(CH_2)_3$-CH=CH-CH_2OH	1.2	73
		CH_3-$(CH_2)_3$-CH_2CH2-CH_2OH		10
20			1.8	60
				10
21			3.2	60
				15

(a). Molar ratio of reagent to substrate for reduction of aldehyde, ketones, acyloins, was 1.5:1

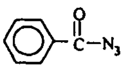
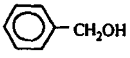
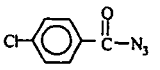
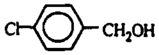
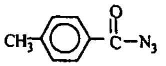
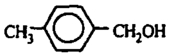
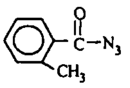
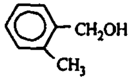
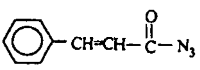
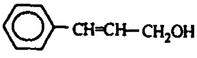
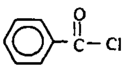
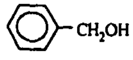
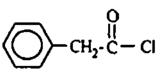
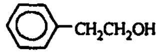
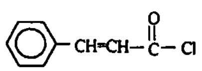
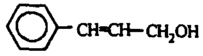
(b). Molar ratio of reagent to substrate for reduction of α- dikitones was 3:1

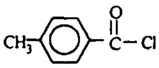
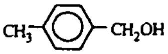
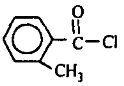
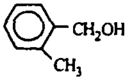
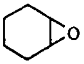
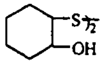
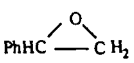
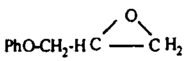
(c). Molar ratio of reagent to substrate for reduction of α,β–unsaturated carbonyl compounds was 2:1

2. Reduction of Carboxylic Acid Chlorides and Aroyl Azides

Reduction of acyl chlorides was also studied with this reagent in THF under reflux conditions. The reaction produced the corresponding alcohols in high yields (87–91%). Attempts for the direct reduction of acyl chlorides to their corresponding aldehydes in a variety of solvents at different temperatures and with different molar ratios of the reducing agent were unsuccessful (Table II). Aroyl azides were also converted to their corresponding alcohols in good yields (85–91%) in dry THF under reflux conditions with short reaction times (Table II).

TABLE II Reduction of Aroyl Azides[a], Acid Chlorides[a], and Ring Opening of Epoxides[b] with $Ca(BH_2S_3)_2$ in Dry THF

Entry	*Substrate*	*Product*	*Time (h)*	*Yield %*
1			2	86
2			2	87
3			1.2	91
4			2.5	85
5			2.2	87
6			2	88
7			2	91
8			2	88

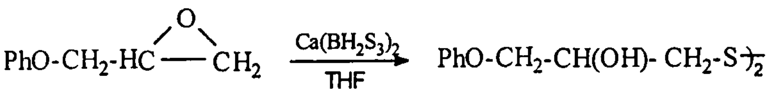
Entry	*Substrate*	*Product*	*Time (h)*	*Yield %*
9			2	91
10			2	87
11			2	82
12		$PhCH(OH)\text{-}CH_2S\text{-})_2$	1.2	84
13		$PhO\text{-}CH_2\text{-}CH(OH)\text{-}CH_2S\text{-})_2$	2	87

(a). Molar ratio of reagent to substrate was 1.5:1 and reactions were carried out under reflux conditions.

(b) Molar ratio of reagent to substrate was 1.5:1 and reactions were carried at room temperature.

3. Ring Opening of Epoxides

Reports for reductive cleavage of epoxides for the synthesis of alcohols with modified borohydrides are available in the literature.[3a] $Ca(BH_2S_3)_2$ however, is an effective reagent for this purpose and the ring opening reaction occurs from the least hindered site of the molecule. In this reaction, the sulfide ion appears to be more available than the hydride ion (Scheme 1) and symmetrical dihydroxydisulfides are obtained (Table II) in high yields. The same reaction has been observed by using $NaBH_2S_3$.



SCHEME 1

CONCLUSION

In this study we have investigated the effect of cation exchange upon the stability and reactivity of $BH_2S_3^-$ moiety in modified sulfurated borohydrides such as $Be(BH_2S_3)_2$, $Mg(BH_2S_3)_2$, and $Ca(BH_2S_3)_2$. Our observations show that the sequence of the stability is $Ca^{+2}>Be^{+2}>Na^{+}>Mg^{+2}$, and the reactivity of $Ca(BH_2S_3)_2$is higher than that of $NaBH_2S_3$. We have applied $Ca(BH_2S_3)_2$ as a new reducing agent for the reduction of aldehydes, ketones, α-hydroxy carbonyl compounds, α-diketones, acyl chlorides, acyl azides, azides, nitro compounds, and epoxides with success in dry THF. High regioselectivity has been observed for the 1,2- versus 1,4-reduction of α,β-unsaturated carbonyl compounds.

EXPERIMENTAL

General

Products were characterized by comparison of their physical data with those of authentic samples. All yields refer to isolated products. IR spectra were recorded on a Perkin Elmer 781 spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX instrument (250 MHZ). Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. Melting points were determined in open capillaries with a Galen-Kamp melting point apparatus. TLC accomplished the purity determination of the substrates and reactions monitoring on silica gel polygram SILG/UV 254 plates.

Preparation of Calcium Sulfurated Borohydride

Sodium borohydride (3.78 g, 0.1 mol) and sulfur (9.6 g, 0.3 mol) was thoroughly mixed under a nitrogen atmosphere in a three-necked flask (250 ml) bearing a condenser and a dropping funnel containing anhydrous THF (50 ml). THF was rapidly added to the dry solid mixture, upon which a brisk exothermic reaction with evolution of hydrogen gas ensues. The flask was kept cool in an ice water bath and under a N_2 atmosphere. After the initial reaction had subsided (~15 min), stirring at 25°C was continued for another 30 min. To the resulting suspension, freshly fused $CaCl_2$

(5.55 g, 0.05 mol) was added. The reaction mixture was magnetically stirred for 24 h at room temperature. Careful evaporation of the solvent under vacuum gave $Ca(BH_2S_3)_2$ in a quantitative yield.

The preparation of beryllium and magnesium analogues followed a similar procedure as described above.

Reduction of Benzaldehyde to Benzyl Alcohol with $Ca(BH_2S_3)_2$. A Typical Procedure

To a suspension of $Ca(BH_2S_3)_2$ (0.57 g, 1.5 mmol) in anhydrous THF (10 ml) in a round bottomed flask (25 ml) equipped with a magnetic stirrer, benzaldehyde (0.107g, 1mmol) in THF (5 ml) was added dropwise. The resulting mixture was stirred and refluxed for 0.8 h. Progress of the reaction was monitored by TLC (eluent; CCl_4/acetone 4/1). After completion of the reaction, the reaction mixture was evaporated to dryness under reduced pressure at room temperature. The residual solid was covered with $CHCl_3$ (15 ml) and then hydrolyzed by HCl solution (10%, 20 ml). The precipitated sulfur was filtered off and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and careful evaporation of the solvent gave benzyl alcohol (0.09 g, 83%).

Reduction of ketones, acid chloride, aroyl azides, acyloins and α- diketones were done as described above. Molar ratios, reaction times and the temperature of the reactions are indicated in Table I, II.

Ring Opening of 3-Phenoxy-1-Propene Oxide to Bis-(3-Phenoxy-2-Hydroxypropyl) Disulfide with $Ca(BH_2S_3)_2$. A Typical Procedure

$Ca(BH_2S_3)_2$ (0.57g, 1.5 mmol) was suspended in dry THF (10ml) and 3-phenoxy-1-propene oxide (0.15g, 1mmol) in THF (5 ml) was added to the suspension. The mixture was stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated to dryness under reduced pressure at room temperature. The residual solid was hydrolyzed by NaOH solution (10%, 20 ml) then filterred and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and careful evaporation of the solvent gave disulfide (0.318 g, 87%) (Table II).

Acknowledgements

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