

Reductions of Functional Groups with Sulfurated Borohydrides. Application to Steroidal Ketones

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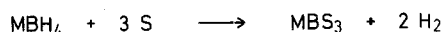
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Sulfurated borohydrides can be prepared very easily from the corresponding borohydrides. These sulfurated borohydrides show selective properties as reducing and sulfurating agents that offer real synthetic interest. A review of the reactions of the main functional groups with NaBH_2S_3 is presented, along with the reductions observed with steroidal ketones.

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This paper summarizes the preparative reactions leading to the formation of stable borohydrides incorporating sulfur, selenium, and tellurium and describes the distinctive reducing properties observed with this new class of compounds.

The reactions between borohydrides and sulfur have received little attention. Chopin and Hagenmuller¹ reported the reaction of NaBH_4 with sulfur at high temperature to proceed according to Scheme A, whereas Noëth and Mikulashek² described a rather unstable species obtained by the addition of sulfur to NaBH_4 at low temperature.



M = Na, K

Scheme A

We have found that by using an appropriate solvent and under mild experimental conditions, sulfur could be reacted with borohydrides to give stable sulfurated hydrides with the evolution of half the hydrogen of the starting hydride. The reduction of several functional groups has been achieved with such sulfurated borohydrides, mainly sulfurated sodium borohydride. Typical results of these reductions are presented in this paper including a study of the reduction of steroidal ketones.

¹ F. CHOPIN, P. HAGENMULLER, *Bull. Soc. Chim. France* **1965**, 3031.

² H. NOËTH, G. MIKULASHEK, *Z. Anorg. Allgem. Chem.* **311**, 241 (1961).

³ J. M. LALANCETTE, A. FRÊCHE, R. MONTEUX, *Can. J. Chem.* **46**, 2754 (1968).

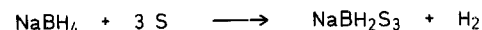
- 2.3. Reduction of Functional Groups incorporating Nitrogen
- 2.4. Preparation of Thioacetals
- 2.5. Reactions of NaBH_2S_3 with Epoxides
- 2.6. Reduction of Carboxylic Acid Derivatives
- 2.7. Selective Reduction of Aldehydes and Ketones
- 2.8. Reduction of Steroidal Ketones

Sulfurierte Borhydride können leicht aus den entsprechenden Borhydriden hergestellt werden. Die sulfurierten Borhydride zeigen in Reduktions- und Sulfurierungsreaktionen eine präparativ interessante Selektivität. In dieser Übersicht werden die Herstellung schwefel-, selen- und tellurhaltiger Borhydride und ihre Reaktionen mit verschiedenen funktionellen Gruppen besprochen.

1. Preparation of Borohydrides incorporating Sulfur, Selenium, or Tellurium

1.1. Sulfurated Sodium Borohydrides

The preparation of sulfurated borohydrides has been described³ and is quite simple. A mixture of one mole of the borohydride and three moles of sulfur is treated with anhydrous tetrahydrofuran. In the presence of this solvent (a few drops will initiate the reaction), a brisk gas evolution starts immediately and after 15 min, half the hydrogen of the hydride is evolved according to Scheme B.



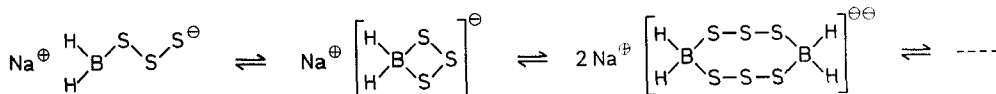
Scheme B

A higher sulfur to hydride ratio does not affect the reaction, the excess of sulfur being recovered unreacted. With a lower ratio, the reaction is incomplete.

Preparation of Sulfurated Sodium Borohydride:

Sodium borohydride (7.56 g, 0.20 mol) and sulfur (19.20 g, 0.60 mol) are thoroughly mixed in a three-neck 1000-ml flask bearing a condenser and a dropping funnel containing anhydrous tetrahydrofuran (50 ml). As the tetrahydrofuran is rapidly added to the dry solid mixture, a brisk exothermic reaction with evolution of hydrogen gas ensues. In the absence of a cold water bath, the solvent reaches the boiling point, however, using a cold water bath the temperature of the well stirred reaction mixture is easily controlled. The evolution of hydrogen ceases after ~ 15 min and the reducing mixture consisting of a suspension of partially dissolved NaBH_2S_3 in tetrahydrofuran is ready for use. To this reducing mixture, a solution of the desired substrate in tetrahydrofuran is simply added. All manipulations are carried out under nitrogen.

By careful evaporation of the solvent it has been possible to isolate the solid sulfurated borohydride and to determine its structure. It has thus been shown that two hydrogens and at least one sulfur atom are bound to boron as indicated in Scheme C.



Scheme C

The role of solvent in the course of the preparative reaction is not clearly established at the present time. Ethers which are good donors, such as tetrahydrofuran, diglyme, and dioxane, appear to be required for the reaction to proceed. But the capability of at least partially dissolving both sulfur and borohydride might be the sole function of the solvent.

Reductions are normally performed by addition of the substrate directly to the resulting suspension of sulfurated borohydride in tetrahydrofuran (the reducing agent is only partially soluble in THF). As the sulfurated borohydride is very hygroscopic it must be handled with precautions similar to those required for LiAlH_4 . Thus, the use of a nitrogen atmosphere was a standard procedure in the present work, though air, for short periods, did not appear to be too detrimental.

In the course of the work-up of the reaction mixture, intermediate boric esters incorporating sulfur have to be hydrolyzed. This is done by a short contact with water. The reaction is complete after a few minutes. The ease of elimination of sulfur present in the system is much influenced by the method of hydrolysis. Organic phases free from sulfur have been easily obtained with 5% sodium hydroxide solution as agent for hydrolysis, the sulfur being extracted in the form of sodium polysulfide into the aqueous phase. Acid hydrolysis has a tendency to induce precipitation of elemental sulfur. Since the hydrolysis of NaBH_2S_3 produces sodium hydroxide, hydrolysis by water in some cases generates a solution basic enough to insure complete elimination of sulfur from the organic fraction.

Reduction with Sulfurated Borohydrides:

The reduction of a desired substrate was accomplished using the above general procedure and adjusting temperature, reaction time, and mole ratio of reducer to substrate as required. The hydrolysis of the reaction mixture may be effected by employing dilute mineral acid, water, or dilute sodium hydroxide solution. In order to minimize product contamination by elemental sulfur, aqueous 5% sodium hydroxide solution is recommended. In the case of this reagent, sulfur is found only in the aqueous phase in the form of polysulfide. If basic conditions had to be avoided, water or dilute mineral acid were employed and it was generally found that the organic phase contained small amounts of sulfur. The sulfur was eliminated by filtration after concentration of the solvent.

N.M.R. measurements were made with a Varian, A 60 apparatus. I.R. measurements were made with a Perkin-Elmer, model 137 spectrophotometer. Melting points were determined on a Büchi apparatus and are not corrected. Polarimetric measurements were made on a Carl Zeiss digital polarimeter.

1.2. Borohydrides Incorporating Selenium and Tellurium

Borohydrides of lithium, sodium, potassium, and tetramethylammonium have been reacted with selenium and tellurium in diglyme⁴. With selenium, the reaction was quite brisk with LiBH_4 , gave the expected NaBH_2Se_3 with NaBH_4 , and less definite compounds with the other two borohydrides. In the case of tellurium, only NaBH_4 led to a definite compound: NaBH_2Te_3 , LiBH_4 giving an explosive reaction and the other borohydrides showing rather sluggish reactivity.

The two borohydrides incorporating the lower chalcogens and having a definite composition: NaBH_2Se_3 and NaBH_2Te_3 , appeared to be even more reactive than NaBH_2S_3 . Though they offer interesting possibilities for incorporating selenium and tellurium into organic substrates their application is somewhat hampered because of the evil smelling mixtures generated.

2. Reactions with Sulfurated Borohydrides

2.1. Reduction of Aldehydes

Aromatic or aliphatic aldehydes are reduced with NaBH_2S_3 to either the corresponding primary alcohol or to a mixture of the primary alcohol and the corresponding disulfide depending on the reaction temperature according to Scheme D. At low temperature ($\sim 0^\circ$), NaBH_2S_3 exhibits typical metallic hydride behavior and results in quantitative yields of primary alcohol. At high temperature ($\sim 60^\circ$ or reflux), however, mixtures of primary alcohol and the corresponding disulfide are produced. Conversions of aldehyde to disulfide as high as 50% have been realized, high conversion being directly proportional to the ease of oxidation of the corresponding alcohol to the starting aldehyde. This high temperature reduction of aldehydes by NaBH_2S_3 offers an interesting new route to the synthesis of disulfides.

⁴ J. M. LALANCETTE, A. FRÊCHE, *Can. J. Chem.* **48**, 2366 (1970).

⁷ B. MAGNUSSON, *Acta. Chem. Scand.* **13**, 1031 (1959).

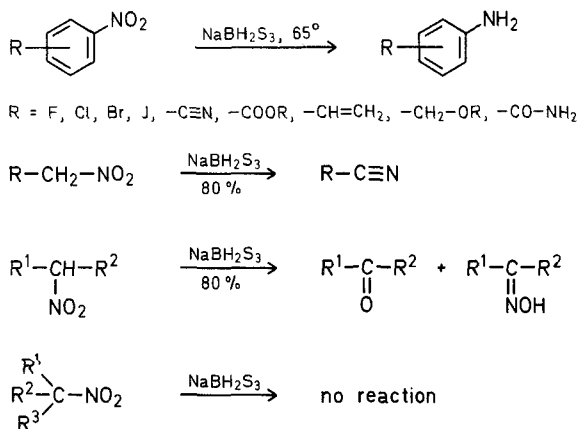
⁸ J. M. LALANCETTE, J. R. BRINDLE, *Can. J. Chem.* **49**, 2990 (1971).

⁹ J. M. LALANCETTE, J. R. BRINDLE, *Can. J. Chem.* **48**, 735 (1970).

⁴ J. M. LALANCETTE, M. ARNAC, *Can. J. Chem.* **47**, 3695 (1969).

⁵ J. M. LALANCETTE, A. FRÊCHE, *Can. J. Chem.* **47**, 739 (1969).

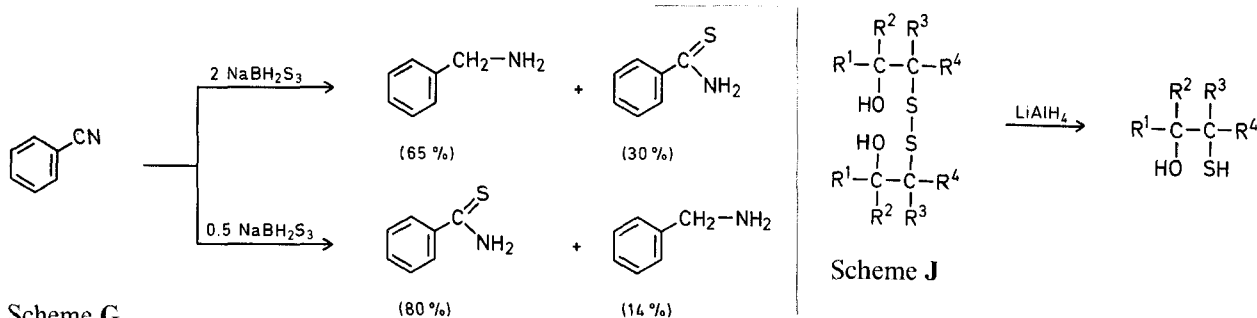
The aliphatic nitro derivatives give even more surprising results with NaBH_2S_3 . In primary nitro derivatives, the nitro group is transformed into the corresponding nitrile. However, secondary nitro compounds are converted into a mixture of ketone and parent oxime and tertiary nitro groups appear to be inert. These reactions in the aliphatic series give acceptable yields and present a unique one-step access to nitriles and ketones from the corresponding nitro derivatives. Scheme F gives a summary of the reactions of nitro groups with NaBH_2S_3 .



Scheme F

Nitro groups can be reduced in the presence of nitriles, without interference with the $\text{C}\equiv\text{N}$ function. But aromatic nitriles are attacked in the absence of the more reactive nitro group⁸. The corresponding thioamide is obtained with an excess of nitrile or the amine with an excess of NaBH_2S_3 , as shown by Scheme G.

Oximes can be reduced to the corresponding amines with yields that vary with the steric hindrance around the site of the reaction, yields ranging from 90% for benzaldoximes to 10% for 4-*t*-butylcyclohexanone oxime⁹. With short contact time, it is possible to stop the reduction at the level of the hydroxylamine but the yield of this intermediate remains at a modest value, around 25%.

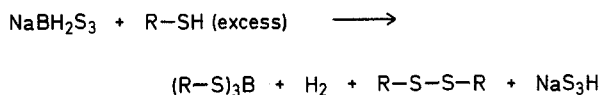


Scheme G

Scheme J

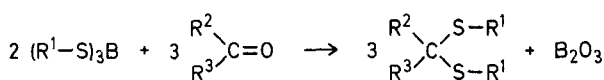
2.4. Preparation of Thioacetals

The reaction of NaBH_2S_3 with mercaptans (Scheme H) leads to the production of orthothioborates $(\text{RS})_3\text{B}$ which can be isolated very easily by distillation if due care is taken to exclude moisture¹⁰.



Scheme H

It has been shown that orthothioborates can be reacted with aldehydes or ketones to give the corresponding thioacetals in good yield, according to Scheme I¹⁰.

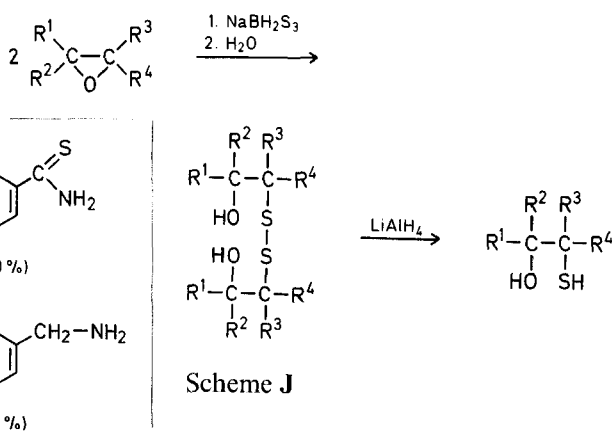


Scheme I

This method of formation of thioacetals is interesting because the reaction is performed under neutral conditions, in benzene or petroleum ether for example, thus avoiding the acid catalysis normally required for the preparation of such a derivative. The spontaneous precipitation of boric anhydride facilitates the experimental procedure. After a short contact time and subsequent filtration, the expected derivative is obtained in good yield (85%).

2.5. Reactions of NaBH_2S_3 with Epoxides

Epoxides are normally cleaved by reaction with alkali metal hydrides to give the corresponding alcohols. With NaBH_2S_3 however, the sulfide chain appears to be more available than the hydride ion and symmetrical dihydroxydisulfides are obtained, according to Scheme J.

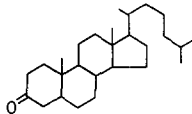
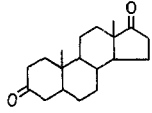
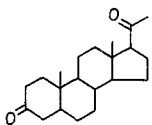
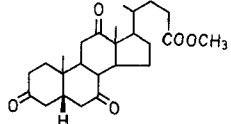
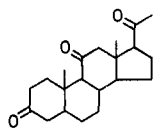
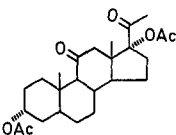
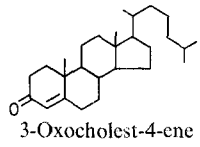
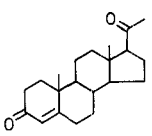
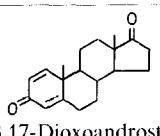


The reaction is general and gives yields of the order of 80%, the sulfur being found at the less hindered side of the molecule. The stereochemistry of the reaction has been established¹¹ and the products have been found to be uniquely *trans*. 1,2-Mercaptols have

¹¹ J. M. LALANCETTE, A. FRÊCHE, *Can. J. Chem.* **49**, 4047 (1971).

¹² C. W. SHOPPEE, G. H. R. SUMMERS, *J. Chem. Soc.* **1950**, 687.

Table 1: Reduction of Steroidal Ketones

Ketone	Reductions with LiAlH ₄ and NaBH ₄				Ratio >C=O/NaBH ₂ S ₃	Reaction time and temperature
	Reducing agent	Alcohols	Yields %	Refer-ences		
 5α-Cholestan-3-one	LiAlH ₄	3α-ol 3β-ol	4 91	12	1/1	3 hr, 25°
	NaBH ₄	3α-ol 3β-ol	13 84	13	2/1	48 hr, 25°
 5α-Androstane-3,17-dione	NaBH ₄	3β-ol 3β,17β-diol	45 5	14	1/1	3 hr, 25°
	NaBH ₄ / pyridine	3α-ol 3β-ol	4 55	14		
 5α-Pregnane-3,20-dione	NaBH ₄	3β-ol	76	15	1/1	3 hr, 25°
					1/2	23 hr, 25°
 3,7,12-Trioxocholanic acid methylester					1/1	5.5 hr, 25°
					1/2	18 hr, 25°
 3,11,20-Trioxo-5α-pregnane	LiAlH ₄	3β,11β,20β-triol	74	17	1/1	5.5 hr, 25°
	NaBH ₄	3β-ol 3α-ol	49 7	16		
	NaBH ₄ / pyridine	3β-ol (from 3,11,20-tri-oxopregnane)	62	15		
 3α,17α-Diacetoxy-11,20-dioxo-5β-pregnane					1/1	68 hr, 20°
					1/2	96 hr, 25°
					1/3	17 hr, 65°
 3-Oxocholest-4-ene	LiAlH ₄	3β-ol 3α-ol	72 16	13	1/2.2	12 hr, 25°
	NaBH ₄	4-ene-3β-ol 4-ene-3α-ol	69 24	13		
 3,20-Dioxopregn-4-ene	LiAlH ₄	4-ene-3β,20β-diol	—	20	1/2.2	12 hr, 25°
	NaBH ₄	4-ene-3β-ol-20-one 4-ene-20β-ol-3-one 4-ene-3β,20β-diol	25 31 7	19 18		
	NaBH ₄ / pyridine	3β-ol-20-one	60	19		
 3,17-Dioxoandrosta-1,4-diene					1/1.1 1/2.5	24 hr, 65° 48 hr, 25°

^a 100% indicates complete reduction of the 3-keto group.

^b ±5%.

^c corrected m. p.

^d Identified by comparison (I. R., N. M. R.) with an authentic sample.

^e Isolated and characterized as acetate.

Reductions with NaBH ₂ S ₃						
Conversion ^a %	Alcohols	Yields ^b %	m. p.		[α] _D (solvent)	
			found	Lit.	found	Lit.
100	3α-ol 3β-ol	8 92	179–182° 142–143°	181–182° 142–143°	— +24 (chloroform)	— +23 ± 2 (chloroform)
50	3α-ol 3β-ol	10 90	d d	d d	— —	— —
100	3α-ol 3β-ol 3β,17β-diol	0 100 0	— 170–172° —	182–183° ^c 174° ^c 163–164° ^c	— +82 dioxan) —	— +81 ± 1 (dioxan) —
100	3β,20β-diol 3β-ol 5α-ol	0 90 0	— 192–194° —	195–196° 191–192° 176°	— +92 (ethanol) —	— +96 ± 4 (ethanol) —
100	3β-ol	90	d	d	d	d
100	3α-ol 3β-ol	90 —	161–162° ^c —	163–164° ^{c,c} —	+58 (dioxan) ^c —	+56 ± 2 (dioxan) ^c —
100	3α-ol 3β-ol	90 —	d —	d —	— —	— —
100	3β-ol 3α-ol	90 0	191–193° %	194–196° ^c 160–165°	+112 (chloroform) —	+109 ± 10 (chloroform) —
0	—	0	—	—	—	—
0	—	0	—	—	—	—
0	—	0	—	—	—	—
100	4-ene-3α-ol 4-ene-3β-ol	— 40+	— 131°	83.4° 132°	— +49 (chloroform)	— +48 ± 5 (chloroform)
100	4-ene-3α-ol-20-one 4-ene-3β-ol-20-one	— 50+	— 159–160°	— 155–161°	— +138 (chloroform)	— +136 ± 3 (chloroform)
0	0	0	—	—	—	—
0	0	0	—	—	—	—

been obtained in yields higher than 90% by reduction of the precursor dihydroxydisulfides with LiAlH_4 , a great improvement of the existing methods of preparation of these mercaptols that give rather low yields, of the order of 25%.

2.6. Reduction of Carboxylic Acid Derivatives

Carboxylic acids and some of their derivatives such as esters, acid halides, anhydrides, and amides have been treated with NaBH_2S_3 , at room temperature or at reflux temperature, in tetrahydrofuran. In all cases, even after long reaction times, the starting material was recovered quantitatively and was not reduced, the sole changes induced by the treatment resulting from hydrolysis, in the case of acid halides and anhydrides.

This result is important in an overall assessment of the reducing capacity of NaBH_2S_3 , since it allows, for example, the reduction of a nitro, oxime, or nitrile group in the presence of an ester group.

2.7. Selective Reduction of Aldehydes and Ketones

Aldehydes can be reduced selectively, with NaBH_2S_3 , in the presence of ketones, if the molar ratio of reducing agent to aldehyde is kept at a suitable value. In a typical reaction, a mixture of 1 mol of phenylacetone and 2 mol of benzaldehyde was treated with 1 mol of NaBH_2S_3 at 0° . The reaction mixture contained 1.8 mol of benzyl alcohol and 0.15 mol of 1-phenylpropan-2-ol. This selectivity could also be noted with ketones of different steric and (or) electronic environment. For example, a mixture of 1 mol of reducing agent, 1 mol of acetophenone, and 1 mol of benzophenone, at -20° , gave predominantly (80/12) the expected 1-phenylpropan-2-ol. This selectivity effect was in all cases enhanced by a low reaction temperature.

2.8. Reduction of Steroidal Ketones

With steroidal ketones, the carbonyl at C-3 appears to be the most reactive site. This high reactivity remains even when the C-3 carbonyl is conjugated. The selective reduction of the carbonyl at the C-3 position is possible in the presence of other carbonyls at C-11, C-12, C-17, and C-20. Such a reduction can be done without interference from an ester group at C-17 and C-24.

With a conjugated carbonyl at C-3, the corresponding allylic alcohol is obtained. The reaction is selective if another carbonyl is present at C-20. But with a carbonyl at C-17, a mixture of diols is obtained.

The alcohol obtained by the reduction with NaBH_2S_3 is predominantly the equatorial isomer. The selectivity of NaBH_2S_3 as a reducing agent for steroidal conjugated ketones is similar to the properties reported for sodium borohydride in isopropanol¹⁹.

Selective Reduction of Steroids (Table 1):

The reduction of saturated steroidal ketones by NaBH_2S_3 was accomplished using the general procedure outlined for the other substrates except that the amount of steroid in the experiment was of the order of 0.002 mol, with 5% excess of reducing agent over the equimolar ratio of reducing agent to ketone. The steroid, dissolved in tetrahydrofuran (5 ml), was added to the NaBH_2S_3 reducing mixture at 10° and the resulting reaction mixture stirred at room temperature for 3 hr. The reaction mixture was hydrolyzed with 10% sodium hydroxide solution (2 ml), extracted with chloroform, and the chloroform extract dried (MgSO_4). The dry chloroform solution was evaporated and the crude mixture of alcohols separated by preparative layer chromatography (P.L.C.) employing alumina. M.p., N.M.R., and rotatory measurements confirmed the structures of the recrystallized alcohols obtained in yields of the order of 90%.

In the case of conjugated ketones, the reduction was carried out employing a 0.001 mol scale. Optimum yields of allylic alcohol were obtained employing a 2 : 1 molar ratio of reducing agent to substrate. In general, longer reaction times (8–11 hrs) and the absence of light and air tended to increase the yield of product. It is noted that Na_2SO_4 , rather than MgSO_4 , was used to dry the organic phase after hydrolysis as the latter drying agent promotes the dehydration of the allylic alcohols.

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