Introduction:

Sodium borohydride is a water soluble reducing agent exhibiting unique properties in organic synthesis. It is established as the benchmark reducing agent for aldehydes, ketones, acid chlorides and anhydrides. Over the past 40 years, significant progress has been made to fine-tune borohydride’s chemoselectivity to make it either more selective, or a stronger reductant. Hence, NaBH₄ can be tuned to reduce acid, ester, halide, amide, lacton and lactam functions. Some of these reductions occur by virtue of the in-situ generation of boranes from NaBH₄.

Especially in the last 20 years, sodium borohydride has become established as the reductant of choice in the large-scale synthesis of active ingredient in applications beyond aldehyde/ketone reductions. Also its use as a reductant with good diastereo-selectivity has become more established, e.g. in the ketone reduction of the Statins (Atorvastatin, Fluvastatin).

This data sheet focuses on enhancing borohydride’s reductive selectivity so that it may accomplish reductive aminations in one pot. The following systems are discussed:

1. Neat borohydride ester reductions
2. Sodium triacetoxyborohydride
3. Sodium borohydride with carboxylic acid

For reasons of confidentiality, public information only is discussed. Reaction schemes are often amenable to optimization for a higher-efficiency use of NaBH₄.

For information regarding reductions other than reductive aminations, please do not hesitate to contact Rohm and Haas.

Typical Properties

- Mol. weight: 37.85
- Form: White crystalline solid
- Melting point: Decomposes above 400°C without melting

A comprehensive overview of the physical and chemical properties of sodium borohydride can be found in Rohm and Haas Company’s Sodium Borohydride Digest.

Benefits of NaBH₄ for Reductive Chemistry:

Of the commercially available metal hydrides used for synthetic organic reductions, NaBH₄ enjoys the largest industrial use, with an estimated (equivalent) market share greater than 50%. Some of the benefits of using borohydride chemistry:

- the least expensive metal hydride commercially available (on a hydride equivalent basis)
- safe with regards to storage and use & handling
- industrial implementation requires no or limited equipment investment
- ease of workup (water soluble boron salts)
- ubiquitous solvents such as water and methanol are typically employed
- unique and versatile as a hydride reducing agent for both chemo- and diastereo-selectivity

Product Stewardship

Rohm and Haas offers metal hydride products as part of a comprehensive Product & Services package, including:

- the highest product quality
- the broadest range of product grades
- formulations stable under various transport conditions
- the availability of a choice of package sizes
- safety audits and training
- technical advice with regards to both the safe handling and the cost-efficient synthetic use

Availability

With its 50+ years of manufacturing experience, Rohm and Haas Company is unique as a borohydride supplier by offering the most complete range of products:

- VenPure SF Powder
- VenPure AF granules, VenPure SF granules
- VenPure AF caplets
- VenPure solution, VenPure 20/20 solution
- VenPure Potassium Borohydride
- Organic NaBH₄ solutions available upon request

All products are available in an ample choice of packages, such as metal pails and drums, mini-bulk containers, and tank trucks or railway cars for bulk quantities.
1. Reductive Amination

In the past year a comprehensive review of the advancements in the use of sodium borohydride for the reductive amination/alkylation reaction has been published. In this technical datasheet we intend to highlight some of these advancements\(^1\).

Reductive amination is a technique to alkylate amines. It consists of two subsequent reactions:

1. **condensation** of an amine with an aldehyde/ketone to an imine, with abstraction of water:

\[
\begin{array}{c}
\text{R'NH}_2 + \text{RCHO} \rightarrow \text{R'N=CHR} + \text{H}_2\text{O} \\
\end{array}
\]

2. **reduction** of the imine to the corresponding amine:

\[
\begin{array}{c}
\text{R'N=CHR} \rightarrow \text{R'NH}_2 \\
\end{array}
\]

As compared to S\(_2\)2 substitutions, which are often employed for amine alkylations, reductive aminations have the advantage that they do not favor over-alkylation. In that respect, they have proven to be synthetically useful in the conversion of primary to secondary amines.

2. Reductive Amination with NaBH\(_4\)

2.1 NaBH\(_4\), Alone

Sodium borohydride can reduce imines in the same manner as it reduces carbonyls (aldehydes and ketones). To eliminate the possibility of any carbonyl starting material being reduced in a one-pot synthesis, it is necessary that the carbonyl-amine condensation reaction has come to completion prior to any sodium borohydride being added.

As a result, neat sodium borohydride should be used for alkylation of those amines that show a favorable formation of the imine, or when this equilibrium can be forced to completion. Please find hereunder some of the parameters that determine how imine formation occurs:

Substrates that are known to form imines sluggishly are:
- weakly electrophilic carbonyl groups
- poor nucleophilic amines
- sterically hindered reactive centers

If any of these compounds are present, it is likely that the imine formation will be slow and neat sodium borohydride will not give good yields. One possibility to drive the reaction to the right, is to increase the temperature of the reaction to azeotrope the water away.

It should also be noted that if the starting amine were chiral the final product would also contain a chiral amine.

2.2 Solvent Effects\(^1\):

It has been demonstrated that methanol favors imine formation more than tetrahydrofuran or 1,2 dichloroethane.

\[
\begin{array}{c}
\text{NH}_2 + \text{NH}_2 + \text{H}-\text{X} \rightarrow \text{N} + \text{H}-\text{X} \\
\end{array}
\]

This reaction has been demonstrated on a 100 kg scale without any problems.\(^2\)

2.3 Acidic Additives\(^1\):

The addition of an acid enhances the reactivity of the imine intermediate. Reaction conditions involving acid buffers and sulfuric acid in THF mixtures have been used to demonstrate this technique\(^3\).

2.4 Zinc Salts\(^4\):

Zinc salts such as zinc chloride and zinc trifluoroacetate in an inert solvent such as THF or isopropyl acetate can result in the formation of the final product in high yields. It is believed that this chemistry goes via the *in-situ* formation of zinc borohydride. Indeed, when off-the-shelf Zn(BH\(_4\))\(_2\) is used, then comparably (high) yields are obtained\(^5\).

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2.6 Titanium (IV) Salts
Titanium(IV) salts such as TiCl₄ and Ti(OPr)₄ can be used to promote abstraction of H₂O, thereby improving the formation of the imine intermediate.

\[
\begin{array}{c|c|c|c|c}
\text{R₁} & \text{R₂} & \text{Metal Hydride} & \text{T} & \text{Time} & \text{Yield} & \text{Decomp.} \\
\hline
\text{Ph} & \text{Me} & \text{Zn(BH₄)₂/THF} & 0°C & 0.25h & 82 & 74 \\
\text{NaBH₄/THF} & RT & 20 & 77 & 76 \\
\text{NaBH₄/MeOH} & 0 & 2 & 60 & 49 \\
\end{array}
\]

2.7 Dehydration Agents
Another way to encourage the formation of the imine intermediate is by removing the water formed during the reaction. This can be accomplished by the addition of dehydrating agents such as molecular sieves. Other drying agents that have been used include anhydrous sodium, calcium, and magnesium sulfates. Another method is to azeotrope the water with benzene or toluene.

3. STAB : NaBH(OAc)₃
Sodium triacetoxy borohydrides (STAB) is more selective a reducing agent than NaBH₄: at pH = 5-6, it reduces imines and aldehydes whereas it does not reduce ketones. The seminal work of Abdel-Magid has expanded the understanding of this reductive technology.

Catalytic Hydrogenation, when used for reductive aminations, may have the potential to reduce the -NO₂ or -CN groups. Also, when weak bases such as aniline are employed, the formation of imine intermediate is not favored, which will result in the hydrogenation of the starting carbonyl.

\[
\begin{array}{c|c|c}
\text{O} & \text{NH₂} & \text{Catalytic Hydrogenation} \\
\hline
\text{O} \text{NH₂} & \text{STAB} & 54\% \quad 87\% \\
\end{array}
\]

Cyanoborohydride is a reagent that often appears in the academic literature for reductive aminations. Whereas cyanoborohydride has its value for reductive aminations, there are some issues with regards to its large-scale implementation:
- when an alcoholic solvent is used, cyanoborohydride may generate ketal and acetal by-products
- residual cyanide is an environmental risk

\[
\begin{array}{c|c|c}
\text{O} & \text{NH₂} & \text{Catalytic Hydrogenation} \\
\hline
\text{O} \text{NH₂} & \text{STAB} & 54\% \quad 87\% \\
\end{array}
\]

Pyridine-Borane has been reported to be a possible reagent for reductive aminations. Yields are consistently lower than when using STAB

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\end{array}
\]

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\[
\begin{array}{c|c|c}
\text{SCBH} & \text{STAB} & \text{Pyridine-Borane} \\
\hline
34 & 86 & \text{Pyridine-Borane} \\
\end{array}
\]

STAB is ideal for reductive amination reaction using aliphatic and aromatic aldehydes as well as aliphatic, cyclic, and bicyclic ketones. One of the true strengths of STAB is its ability to accomplish reductive aminations with weakly basic amines, for example, aromatic amines containing withdrawing groups such as -NO₂ and -CN. For such substrates, STAB is unique in its selectivity as compared to catalytic hydrogenation and sodium cyanoborohydride.

Solubility of STAB:
STAB is soluble in carboxylic acids, slightly soluble in ethers, cyclic ethers, and chlorinated hydrocarbons.
Stability of STAB:
STAB will react with protic solvent such as water, and alcohols.

Reactivity of STAB:
The addition of a small amount of acid has been shown to increase the yield of STAB mediated reductive amination reaction.\(^7\)

- Sodium triacetoxy-borohydride (STAB) is formed from the reaction of sodium borohydride with three moles of a acetic acid (AcOH) in an inert solvent such as toluene. Other acids, such as ethyl and propionic acids, may also be used to obtain comparable reducing agents.
- Feel free to contact Rohm and Haas’s Technical Support Team for further details.

In addition to imine reductions, STAB-based technologies have been developed to convert
Lactones to Lactams using near-stoichiometric quantities of starting materials and STAB. Acceptable yields have been reported for alkylamines.\(^8\)

If a carboxylic acid is used as the solvent for a NaBH reaction, then a very effective reductive amination system results. Seminal work by and review by Gribble describes this technology.\(^9\)

It has been demonstrated that, upon addition of acetic acid to NaBH\(_4\), STAB is generated \textit{in situ}. This technique allows for a One Pot / One Step approach.

It has been reported that \textit{in situ} generated STAB is more efficient a reducing system than \textit{ex situ} produced STAB.\(^12\)

4. Sodium Borohydride and Carboxylic Acid

4.1. Sodium Borohydride and Acetic Acid
Sodium triacetoxy borohydride (STAB) is formed from the reaction of sodium borohydride with three moles of acetic acid in an inert solvent such as toluene. The most common acid used is acetic acid. A slight excess of acetic acid will increase the yields of reductive amination.

- Lactams is an important synthon for the synthesis of many drugs such as Neurontin, @-Baclofen, CI-1008, Rolipram, Rolicyprine and gamma-butyric acid.

4.2 Sodium Borohydride, Carboxylic Acid, and Amines
So far, we have only discussed how aldehydes and ketones can be used to alkylate amines. Alternatively, carboxylic acids can be used thereto. As compared to the above described Reductive Amination, the conversion using carboxylic acid includes one additional ketone reduction step. The reaction conditions are similar to the ‘normal’ reductive amination, but somewhat higher reaction temperatures may be required.

- Just as different aldehydes/ketones can be used for different amine alkylations, different acids can be used for the introduction of different alkyl groups: formic acid leads to a methyl group, propionic acid to a propyl group, and butyric acid to a t-butyl group.
Double alkylation using acetic acid and temperature.

Depending on the reaction conditions sodium borohydride with carboxylic acids can be used to either mono- or di- alkylated amines in high yields with the use of a auxiliary carbonyl compound.

The example hereunder shows how an amine is first alkylated by using acetone, and then subsequently by using acetic acid. It is a One Pot / Two Step reaction, whereby the second step consists of merely increasing the temperature.

A final example to illustrate the synthetic capability of *in-situ* STAB generation from NaBH₄ and acetic acid (AcOH):

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4.27 MeNH₂ + EtOH
4) 15h, 2 °C
Yield = 100 % !
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References

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8) Zhang, J.; Blazek, P.G.; Davidson, J.G. *Org. Lett.* 2003, 5, 553