Chapter 11

Sodium Borohydride and Carboxylic Acids: A Novel Reagent Combination

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The combination of sodium borohydride (NaBH₄) and carboxylic acids – sodium acyloxyborohydrides – represents a remarkably versatile and powerfully efficient synthetic tool. This reagent manifold, the reactivity of which can be controlled depending on the nature and number of acyloxy groups, reduces and N-alkylates indoles, quinolines, isoquinolines, related heterocycles, imines, enamines, oximes, enamides, and similar functional groups. It reduces amides and nitriles to amines in the presence of esters, aryl alcohols and ketones to hydrocarbons, aldehydes to alcohols in the presence of ketones, and β-hydroxyketones to 1,3-diols stereoselectively. This reagent is also an extraordinarily useful methodology for the N-alkylation of primary and secondary amines, in a reaction sequence that is believed to involve sequential reduction of the carboxylic acid to the corresponding aldehyde followed by a standard reductive amination process. Frequently, the monoalkylation of primary amines can be achieved. The use of sodium cyanoborohydride (NaBH₃CN) militates against N-alkylation, and, for example, the union of NaBH₃CN/HOAc cleanly reduces indoles to indolines sans alkylation. Depending on the circumstances and conditions, alicyclics can be hydroborated, esters and carboxylic acids can be reduced to alcohols, and arenes can be induced to undergo the Baeyer condensation. No other chemical system can boast of such amazing flexibility!

More than 20 years ago, as part of an undergraduate research project at Dartmouth, we decided to attempt the reduction of 1,2,3,4-tetrahydrocarbazole with neat formic acid. A general indole double-bond reduction method was lacking at that time (I) and we felt that a Leuckart-type reaction (2) on the protonated indole might occur (equation 1). However, the only product of this reaction was the N-formyl derivative of 1 (95%) (Gribble, G. W.; Strickman, D., Dartmouth College, unpublished result).

Nevertheless, since indoles are well known to undergo C-3 protonation in mineral acids (I, 3), we felt that a better hydride source than formate might succeed in ambushing the presumed indolenium ion (e.g., 2), if indeed carboxylic acids are capable of protonating the indole double bond. We chose to study sodium borohydride
9 and 10 were confirmed by independent syntheses and conversion to known compounds. For example, reaction of 9 under these conditions gives 10 in 57% yield.

![Chemical structure](image)

The formation of 10 and the N-alkylation of indoles with NaBH₄/RCO₂H suggested to us that aldehydes, or their synthetic equivalent, were the source of the alkyl group. This pathway is discussed in the next section. As expected, treatment of the N-alkylinoles with NaBH₄/HOAc affords the corresponding N-alkylinoles (equation 5) (7).

![Chemical structure](image)

Since the original goal of this research program was to discover a new indole to indole reduction method, some N-alkylation, we examined the reaction of indole with sodium cyanoborohydride (NaBH₃CN) in HOAc. Much to our delight, this reaction afforded indole (5) in 91% distilled yield, with no trace of N-ethylindole (7, 13). At higher temperatures, N-ethylindole is observed (13, 14). The reaction is rapid, general, and efficient (equation 6), failing only with electron-withdrawing substituents on the indole ring (e.g., 5-nitro- and 2,3-diphenylimidole).

![Chemical structure](image)

This very useful indole reduction method has been employed by many groups and some of the indolines thusly prepared are shown in Scheme 1.
Scheme 1

\[
\text{MeO-} \quad \text{EtO-C} \quad \text{MeO-} \\
\text{H} \quad \text{H} \quad \text{H}
\]

74% (15) 98% (16) 11 96% (17)

\[
\text{MeO-} \quad \text{MeO-} \quad \text{H}
\]

98% (18)

\[
\text{MeO-} \quad \text{MeO-} \quad \text{Me}
\]

(19)

\[
\text{BnO-C} \quad \text{Me}
\]

75% (21)

\[
\text{Et-} \quad \text{N} \quad \text{Me}
\]

12 61% (22)

In particular, this reagent combination has been very successful in the selective reduction of the more basic indole double bond in CC-1065 and PDE precursors (17, 22-27), such as 11 and 12 in Scheme 1. Not surprisingly, treatment of indole with \( \text{NaBH}_4/\text{HOAc} \) in the presence of added acetaldehyde affords \( N \)-ethylindoline in 87% yield (Gribble, G.W. Dartmouth College, unpublished result). Thus, it would appear that \( \text{NaBH}_3 \text{CN} \) is less effective than \( \text{NaBH}_4 \) in generating aldehydes (or their equivalents) from carboxylic acids. Ironically, the first report of the treatment of an indole with \( \text{NaBH}_4/\text{HOAc} \) did not result in the reduction of the indole double bond (equation 7) (28). We believe that this lack of reduction in this and related systems that contain a basic nitrogen (29-31) is due to protonation of the basic nitrogen which prevents a second protonation of the indole double bond.

\[
\text{NaBH}_4 \quad \text{HOAc} \\
\text{H} \quad 25^\circ \text{C}
\]

62% + lactone (7)

Indeed, we found that TFA in combination with \( \text{NaBH}_4 \) smoothly reduces basic indoles such as indolo[2,3-\( \alpha \)]quinolizidines (equation 8) (32).

\[
\begin{align*}
\text{N} \quad \text{H} & \quad \text{N} \\
\text{Et} \quad \text{Et} & \quad \text{Et}
\end{align*}
\]

\[
\xrightarrow{\text{NaBH}_4} \text{NHEt} \\
\text{EtCO}_2\text{H} & \quad \text{50}^\circ \text{C} & 70\%
\]

88% \( \text{HOAc} \)

\[
\xrightarrow{\text{NaBH}_4} \text{NH}_2 \quad \text{PhCHO} \\
\text{20}^\circ \text{C} & \quad \text{50-60}^\circ \text{C} & 74\%
\]

1. PhCHO

1. \text{PhCHO}

2. \text{NaBH}_4

NaBH\_4

\[
\begin{align*}
\text{Et-} & \quad \text{N} \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{NHCH}_2\text{C(CH}_3\text{)} & \quad \text{Et-} \quad \text{N} \quad \text{CH}_2\text{Ph}
\end{align*}
\]

This \( N \)-alkylation is general for a range of secondary to tertiary anilines as well as for different carboxylic acids (equation 9) (7, Gribble, G.W. Dartmouth College, unpublished results).
unpublished results), including solid carboxylic acids in a cosolvent (40). Even the
weakly basic carbazole can be N-ethyalted with NaBH$_4$HOAc (92% yield) (7).

![Chemical structures](image)

Although it is generally sluggish, in some cases, the combination of NaBH$_4$/TFA
leads to N-trifluoroethylation of aromatic amines (e.g., equations 10-12) (12, 34, 41).

![Chemical structures](image)

This very useful aromatic amine alkylation has been employed many times in
recent years and a few of the resulting compounds are shown in Scheme 3. In some
cases, the alkyl group is derived from added aldehyde or ketone.

**Scheme 3**

![Chemical structures](image)

We also discovered that the N-alkylation of more basic aliphatic amines could be
accomplished with NaBH$_4$/RCO$_2$H (47). Thus, N-alkylbenzylamines can be N-
ethyalted with NaBH$_4$/HOAc and N-methylbenzylamine can be N-alkylated with
NaBH$_4$/RCO$_2$H (equation 13).

![Chemical structures](image)

Furthermore, N-benzylamine can be manipulated in the same way that aniline
can be (Scheme 2), as summarized in equation 14 (47). The preparation of the
unsymmetrical tertiary amine, N-ethyl-N-i-propylbenzylamine in one pot is
noteworthy.

![Chemical structures](image)

Some additional aliphatic amines that we have N-ethylated using NaBH$_4$/HOAc
are shown in Scheme 4 (47), Gribble, G.W. Dartmouth College, unpublished results).
Only in the case of highly hindered secondary amines or with hindered carboxylic
acids does this alkylation proceed poorly.

**Scheme 4**

![Chemical structures](image)
Longer chain carboxylic acids can be used to alkylate diethylamine and dimethyamine (equations 15, 16) (47).

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{NH} & \xrightarrow{\text{NaBH}_4, \text{CH}_3\text{(CH}_2)_6\text{CO}_2\text{H}, 50-55 \, ^\circ\text{C}} \text{CH}_3\text{CH}_2\text{N}-(\text{CH}_2)_7\text{-CH}_3 \quad (15) \\
\text{CH}_3\text{CH}_2\text{NH} \cdot \text{HCl} & \xrightarrow{\text{NaOAc, THF, CH}_3\text{(CH}_2)_7\text{CO}_2\text{H}, 50-55 \, ^\circ\text{C}} \text{CH}_3\text{N}-(\text{CH}_2)_8\text{-CH}_3 \quad (16)
\end{align*}
\]

Several other examples of the N-alkylation of aliphatic amines have been described in recent years and a few of these are summarized in Scheme 5. In most examples, either an ethyl or n-propyl group has been introduced, and, in some cases, multiple N-alkylation is the objective.

Scheme 5

\[
\begin{align*}
\text{O}_2\text{S} & - n\text{-C}_8\text{H}_{17} \quad 51\% \quad (48) \\
\text{OMe} & \quad 75\% \quad (50) \\
\text{MeO} & \quad 76\% \quad (53) \\
\text{OH} & \quad 74\% \quad (54)
\end{align*}
\]

Because the reaction of NaBH4 with formic acid (HCO2H) is exceptionally vigorous, we have developed an alternative N-methylation protocol that utilizes paraformaldehyde in conjunction with NaBH4/TFA or NaBH3CN/HOAc (55) (equations 17, 18).

\[
\begin{align*}
\text{(PhCH}_2\text{CH}_2\text{)}_2\text{NH} & \xrightarrow{\text{NaBH}_4, \text{TFA, THF}, 87\%} \text{(PhCH}_2\text{CH}_2\text{CH}_2\text{NCH}_3) \quad (17) \\
\text{H} & \xrightarrow{\text{NaBH}_4, \text{CN, HOAc}, 82\%} \quad (18)
\end{align*}
\]

An important variation on this reductive amination methodology has been developed by Abdel-Magid and is presented in a separate Chapter in this volume.

We believe that the mechanism of the N-alkylation of amines with NaBH4/RCO2H involves the in situ generation of a tricycloxyborohydride species, which forms in the presence of excess carboxylic acid and which has been isolated and characterized (7, 9, 40, 41, 56, 57). This material then suffers self-reduction to generate either the free aldehyde or a boron species at the aldehyde oxidation level. Reductive amination of this aldehyde species completes the N-alkylation sequence (Scheme 6). Control experiments reveal that N-acylation is not involved since, for example, neither N-acetylindolone nor N-acytlylindole are reduced to N-ethyldiisole under the reaction conditions (7). However, as will be seen, amides are reduced to amines with the more reactive monitriacyloxyborohydride (vide infra). Support for the intermediacy of aldehydes is the fact that added aldehydes readily undergo reductive amination under the reaction conditions (Gribble, G.W. Dartmouth College, unpublished results), and that acetaldehyde can be trapped as its 2,4-DNP derivative from the evolved gases when NaBH4 reacts with excess HOAc (7).

Scheme 6

\[
\begin{align*}
\text{NaBH}_4 + \text{RCO}_2\text{H} & \xrightarrow{-3\text{H}_2} \text{NaBH}(_3\text{OCR})_3 \xrightarrow{\text{OCOR}} \text{NaB}(_3\text{OCOR}) \xrightarrow{\text{H-C-OH}} \text{R-C-H} \\
\text{reductive} & \text{amination}
\end{align*}
\]

Reduction of Other Heterocycles.

Not surprisingly, a variety of other nitrogen and oxygen heterocycles are reduced and N-alkylated by the action of NaBH4 and RCO2H.

Following an earlier report on the partial reduction of nitroquinolines with NaBH4/HOAc (58), we examined this reaction with quinoline and isoquinoline in some detail (59). These two heterocycles exhibit a similar reaction manifold as summarized for quinoline in Scheme 7. Once again the reaction conditions may be varied to allow or to avoid N-alkylation, and to introduce secondary alkyl groups using a ketone additive.
since ketones are normally not reduced under these conditions. The selective N-ethylation in equation 27 is noteworthy (60).

Acridine is reduced to acridan at 20 °C and converted to N-ethylacridan at higher temperature (equation 21) (Gribble, G.W. Dartmouth College, unpublished results).

Several other examples of the reduction of quinolines and related heterocycles are summarized in equations 22-27 (61-65). The reaction shown in equation 24 involves an interesting migration of the acetyl group (63), and the reduction of the ketone in tryptanthrin (equation 26) (65) may involve amine-directed hydride transfer.

Other examples of imine reduction in nitrogen heterocycles have been uncovered. For example, benzoazoles undergo reductive cleavage (equation 28) (67) and the synthesis of lennoxamine involves imine reduction and subsequent
lactamization of a benzazepine (equation 29) (68). The imine group in a benzodiazepine is selectively reduced in the presence of an indole double bond (equation 30) (69). Presumably, the (protonated) basic nitrogen protects the indole ring towards protonation. A recent study of the reduction of indeno[1,2-b]quinoxalines and benzo[b]phenazines has been reported (e.g., equation 31) (70).

![Chemical structures](image)

In a series of papers, Balaban and his colleagues have utilized NaBH₄/HOAc to reduce pyrrolium salts (equation 32) (71-74).

![Chemical structures](image)

Although our early attempts to reduce simple pyroles were unsuccessful (Gribble, G.W. Dartmouth College, unpublished results), Ketcha has succeeded in reducing N-(phenylsulfonyl)pyrroles with NaBH₃CN/TFA (equation 33) (75). The fully reduced compounds are minor products.

11. Gribble Sodium Borohydride and Carboxylic Acids

\[
\begin{align*}
\text{Sodium Borohydride and Carboxylic Acids} & \\
\text{Saturated heterocycles are reductively cleaved under these conditions, analogous to the reaction of acetics (vide infra). Two examples are shown (equations 34, 35) (76, 77).} & \\
\text{Reduction of Oximes, Imines, Enamines and Related Compounds.} & \\
\text{Not surprisingly, in view of the facile reductions of indole, quinoline, and related heterocycles with NaBH₄/RCO₂H (vide supra), a wide range of C=N compounds are also transformed with these reagents. Moreover, compounds, such as enamines and enamides that can be protonated to form iminium ions are also readily reduced. An earlier review documents many examples of this type (9).} & \\
\text{Oximes can be reduced and N-alkylated under the influence of NaBH₄ and this procedure represents an excellent way to prepare unsymmetrical N,N-dialkylhydroxylamines (78). Three examples are shown (equations 36-38). Once again, alkylation can be suppressed by using NaBH₃CN (equation 38).} & \\
\end{align*}
\]

![Chemical structures](image)

In some cases, over-reduction results (equations 39, 40) (78, 79).
Several workers have exploited this methodology to reduce oximes or oxime ethers and the products of these reactions are summarized in Scheme 8.

Scheme 8

Furthermore, Williams has described the hydroxy-directed reduction of oxime ethers using the isolated reagent NaBH(OAc)$_3$ (equation 41) (86), a powerful tactic that will be discussed again in the reduction of $\beta$-hydroxy ketones.

A number of simple imines are reduced with NaBH$_4$ or NaBH$_3$CN in carboxylic acids, as tabulated in equations 42-44 (87-89).
Several such reductions are known from the indole field (equations 56-59) (104-107), including Djerassi's original observation (equation 7) (28). As expected, the indole double bond is impervious to these reduction conditions.

\[
\text{EtO} \quad \text{NHBN} \quad \xrightarrow{\text{NaBH(OAc)}_3} \quad \text{EtO} \quad \text{NHBN} \quad \text{(51)}
\]

\[
\text{Cl} \quad \text{HCO}_2 \text{H} \quad \xrightarrow{\text{NaBH}_3\text{CN}} \quad \text{Cl} \quad \text{Ph} \quad \text{(52)}
\]

\[
\text{Cl} \quad \text{N}(\text{CH}_2)_1\text{OCH}_3 \quad \xrightarrow{\text{NaBH}_3\text{CN}} \quad \text{Cl} \quad \text{N}(\text{CH}_2)_1\text{OCH}_3 \quad \text{(53)}
\]

\[
\text{N} \quad \text{BOC} \quad \xrightarrow{\text{CH}_2\text{Cl}_2, \text{TFA} \quad \text{H}^+} \quad \text{N} \quad \text{BOC} \quad \text{(54)}
\]

\[
\text{N} \quad \text{Ts} \quad \xrightarrow{\text{CH}_2\text{Cl}_2, \text{TFA} \quad \text{H}^+} \quad \text{N} \quad \text{Ts} \quad \text{(55)}
\]

Reduction of Amides.

It has been seen that amides survive unscathed in the reaction medium presented thus far, which generates NaBH(OCOR)_3 species (excess ROH). Umino and his colleagues discovered that amides are, in fact, reduced to amines under conditions that generate the more reactive NaBH_3OCOR species (108). This important extension of the NaBH_4/ROH technology has been utilized by several groups to reduce amides and lactams (9). A few recent examples are tabulated in equations 60-63 (109-112). The selectivity in equations 61 and 63 is noteworthy, and the latter reduction is thought to involve hydroxyl participation since the OTBS ether is not reduced (112).

\[
\text{NaBH}_4 \quad \xrightarrow{\text{HOAc, dioxane}} \quad \text{(60)}
\]
Reduction of Nitriles.

Umino also discovered that nitriles can be reduced to primary amines with NaBH$_3$OCCCF$_3$, but poorly with NaBH$_3$OAc (113). A few recent cases are shown here (equations 64-68) (114-117, Gribble, G.W. Dartmouth College, unpublished results). The lack of nitro group reduction is particularly noteworthy since conventional reduction methods would invariably reduce the nitro group before the cyano group.

\[
\text{Me} - \text{N} - \text{Cl} - \text{CN} \xrightarrow{\text{NaBH}_3\text{OCCCF}_3, \text{THF}, 10-15^\circ C} \text{Me} - \text{N} - \text{Cl} - \text{NH}_2
\]

(64)

\[
\text{CN} \xrightarrow{\text{NaBH}_3\text{OCCCF}_3, \text{THF}, rt} \text{NH}_2
\]

(65)

\[
\text{O} - \text{O} - \text{CN} \xrightarrow{\text{NaBH}_3\text{OCCCF}_3, \text{THF}, rt} \text{O} - \text{O} - \text{CH}_2\text{NH}_2
\]

(66)

Hydroboration of Alkenes.

Marshall and Johnson also described the use of NaBH$_4$/HOAc to hydroborate alkenes (119), and several recent examples and variations have been reported (9). A few recent examples are illustrated in equations 70-72 (120-122). The NaBH$_3$OAc in equations 70 and 71 can also be generated from NaBH$_4$ and Hg(OAc)$_2$ (120, 121). In related chemistry, organomercurials can be reduced with NaBH$_4$(OAc)$_3$ (123).

\[
\text{Ph} = \text{OH} \xrightarrow{\text{1. NaBH}_4, \text{HOAc}, 2. \text{H}_2\text{O}_2, \text{OH}^-} \text{Ph} = \text{OH}
\]

(70)

\[
\text{OTMS} \xrightarrow{\text{1. NaBH}_3\text{OAc}, 2. \text{H}_2\text{O}_2, \text{OH}^-} \text{OTMS}
\]

(71)

\[
\text{Me} \xrightarrow{\text{1. NaBH}_3\text{OAc}, 2. \text{NaOMe}, 3. \text{H}_2\text{O}_2, \text{OH}^-} \text{Me}
\]

(72)

Reduction of Alkenes.

In addition to hydroboration, alkenes can be reduced to alkanes in a few cases. The first such example was our observation that 1,1-diphenylethylene was reduced to 1,1-diphenylethane with NaBH$_4$/TFA in 93% yield, undoubtedly via the highly stabilized carbocation (124). However, only a few other examples of alkene reductions with NaBH$_4$/RCO$_2$H have been reported (e.g., equations 73, 74) (125, 126).
Reduction of Alcohols.

Early in our research program, when we realized that trifluoroacetic acid (TFA) and NaBH₄ were reasonably compatible, we thought that benzylic alcohols would be reduced to hydrocarbons under these conditions, since TFA is an excellent solvent for solvolysis and other Sw1 reactions (ionizing power Y value = 1.84). Indeed, diphenylmethanol and triphenylmethanol are reduced to diphenylmethane and triphenylmethane in 93% and 99% yields, respectively (124). The reaction is very general for diaryl- and triarylcarbinols but is poorer for monobenzylic alcohols (9, 124) where the more reactive intermediate carbocations undergo side reactions (9). However, Nutaitis has found that the more reactive NaBH₄OCOCF₃ can reduce certain monobenzylic alcohols (equation 75) (127). Secondary and tertiary monobenzylic alcohols give higher yields.

Some other recent examples of the reduction of monobenzylic alcohols are cited in equations 76-78 (128-130). Interestingly, Olah has found that NaBH₄/CF₃SO₂H is even more effective (98%) in reducing the alcohol shown in equation 77 (129). The selective deoxygenation shown in equation 78 is remarkable indeed (130).
Nicholas has shown that acetylenic diol cobalt complexes are smoothly deoxygenated with NaBH₄/TFA (equations 82, 83) (138, 139).

\[
\begin{array}{c}
\text{CO}_2\text{(CO)}_6 \xrightarrow{\text{1. NaBH}_4 / \text{TFA}} \text{Et} \quad \text{Et} \\
\text{OH} \quad \text{OH} \\
\xrightarrow{\text{2. Fe(NO}_3)_3} \quad \text{Et} \\
\text{HO} \quad \text{CO}_2\text{(CO)}_6 \\
\text{C} \quad \text{C} \\
\text{Et} \quad \text{C} \\
\text{(82)} \\
\end{array}
\]

The enormous power and versatility of the NaBH₄/TFA reducing system is beautifully revealed by the comparison reactions discovered by Maryanoff and his colleagues (equations 84, 85) (140). In the first reaction, the alcohol is reduced by NaBH(OOCOCF₃)₃ in the presence of excess TFA, but, in the second reaction, the more reactive NaBH₃OCOCF₃ reduces only the lactam since excess TFA is not present.

\[
\begin{array}{c}
\text{Ph} \quad \text{OH} \\
\xrightarrow{\text{NaBH}_4 / \text{TFA}} \text{Ph} \\
\text{major} (87:13) \\
\text{(84)} \\
\end{array}
\]

Reduction of Ketones to Hydrocarbons.

During our early research on the reduction of diarylmethanoles to diarylmethanes (124) (vide supra), we also discovered that benzophenone is reduced to diphenylmethane with NaBH₄/TFA in 92% distilled yield (124). Subsequent studies in our laboratory revealed the generality of this novel and efficient reduction method (equation 86) (141). A range of functional groups tolerates these reaction conditions and the reaction only fails or fares poorly when the ketone is highly hindered (dimethyl ketone) or contains a nitro group (141).

\[
\begin{array}{c}
\text{R} \quad \text{O} \\
\xrightarrow{\text{NaBH}_4 / \text{TFA}} \text{R} \\
\text{CH}_2\text{Cl}_2 \quad 15-20 \, ^\circ \text{C} \\
\text{H}_2 \text{C} = \text{C} \quad 73-94\% \\
\text{R} = \text{H, Me, OH, OMe, Br,} \\
\text{F, CN, CO}_2\text{Me, CO}_2\text{H,} \\
\text{NHCOPh, NMe}_2 \\
\text{(86)} \\
\end{array}
\]

Some recent compounds that have been synthesized by the action of NaBH₄/TFA on the corresponding ketone (indicated by an arrow) are listed in Scheme 10. The NaBH₃CN/TFA reaction leading to the pyrrole imide (147) appears to be the first reduction of a formyl group to a methyl group using this methodology.

**Scheme 10**

The reaction of 2-ido-3-acetyl-\(N\)-(phenylsulfonfonyl)indole with NaBH₄/TFA gives 3-ethyl-\(N\)-(phenylsulfonfonyl)indole (75% yield) (145). This appears to be the first example of dehalogenation with NaBH₄/RCO₂H.

In related chemistry discovered sometime ago, Hutchins utilized NaBH₄/HOAc to reduce the tosylhydrzones of aldehydes and ketones to hydrocarbons (149). A recent example of this reaction is shown in equation 87 (150).

\[
\begin{array}{c}
\text{HO} \\
\xrightarrow{\text{NaBH}_3\text{CN}} \text{HO} \\
\text{70 \, ^\circ \text{C}} \\
\text{56\%} \\
\end{array}
\]
Reduction of Carboxylic Acids and Esters.

In view of the facile reduction of carboxylic acids to aldehydes with NaBH₄, via acyloxyborohydrides, it is not surprising that complete reduction to primary alcohols has been observed by two groups (equations 88, 89) (151, 152), following the pioneering work by Liberatore and colleagues (40).

\[
\begin{align*}
\text{CO}_2\text{H} & \xrightarrow{\text{NaBH}_4} \text{CO}_2\text{H} \xrightarrow{\text{TFA}} \text{MeO}^\cdot \xrightarrow{\Delta} \text{MeO}^\cdot \\
\text{O} & \xrightarrow{\text{NaBH}_4} \text{MeO}^\cdot \xrightarrow{\text{TFA}} \text{MeO}^\cdot \xrightarrow{\text{THF}} \text{MeO}^\cdot
\end{align*}
\]

(88)

(89)

The only report of the NaBH₄/RCO₂H reduction of an ester group appears to be that shown in equation 90 (and related examples) (153).

\[
\begin{align*}
\text{CO}_2\text{Me} & \xrightarrow{\text{NaBH}_4} \text{HN}^\cdot \xrightarrow{\text{HOAc}} \text{MeO}^\cdot \\
\text{HN}^\cdot & \xrightarrow{\text{dioxane}} \text{HN}^\cdot \\
\text{MeO}^\cdot & \xrightarrow{25 ^\circ \text{C}} \text{MeO}^\cdot \\
\text{HN}^\cdot & \xrightarrow{80 ^\circ \text{C}} \text{HN}^\cdot \\
\text{MeO}^\cdot & \xrightarrow{90 ^\circ \text{C}} \text{MeO}^\cdot
\end{align*}
\]

90)

Reductive Cleavage of Acetals, Ketals and Ethers.

As might be anticipated, the action of NaBH₄/RCO₂H affects the cleavage of acetals, ketals, ethers and related compounds (9). We have reported both the reductive cleavage of cyclic acetals and ketals (e.g., equation 91) (154) and the reductive deoxygenation of 1,4-epoxy-1,4-dihyronaphthalenes (e.g., equation 92) (155). We utilized the latter reaction in the synthesis of a dimethylbenzo[β]carbazole (equation 93) (156).

\[
\begin{align*}
\text{O} & \xrightarrow{\text{NaBH}_4} \text{HN}^\cdot \xrightarrow{\text{TFA}} \text{MeO}^\cdot \\
\text{O} & \xrightarrow{\text{NaBH}_4} \text{Me} \xrightarrow{\text{TFA}} \text{Me} \\
\text{Me} & \xrightarrow{\text{N}^\cdot} \text{PhO}_2^\cdot \\
\text{Me} & \xrightarrow{\text{NaBH}_4} \text{Me} \xrightarrow{\text{TFA}} \text{Me} \\
\text{OMe} & \xrightarrow{\text{NaBH}_4} \text{Me} \xrightarrow{\text{TFA}} \text{Me}
\end{align*}
\]

91)

92)

93)

Selective Aldehyde Reduction

Early in our work with NaBH₄/RCO₂H, we observed that aldehydes and, especially, ketones are reduced much more slowly to alcohols by NaBH₄/HOAc than in conventional alcoholic or aqueous media. Indeed, this is why the N-alkylation of amines in this medium is successful! For example, although benzaldehyde is completely reduced to benzyl alcohol after 1 hr at 15 °C with a large excess of NaBH₄ in glacial HOAc, acetophenone is only reduced to the extent of 60% at 25 °C after 40 hr (9, Gribble, G.W. Dartmouth College, unpublished results).

These and related observations paved the way for the chemoselective reduction of aldehydes, in the presence of ketones. We found that the isolated reagents (NaBH(OAc)₃ (56) or α-Bu₄NBH(OAc)₃ (159) in benzene worked extremely well in this regard (equations 95-97). For other examples, see ref. 9.
More recently, other workers have exploited this method for the selective reduction of aldehydes in the presence of ketones (Scheme 12). In each case, the primary alcohol was derived from the corresponding ketoaldehyde using NaBH(OAc)$_3$ in benzene.

Scheme 12

Intrinsically more reactive ketones (cyclic, $\alpha$- and $\beta$-keto) are reduced by NaBD$_3$/RCOO$_2$H and some recent examples are shown in equations 98-100 (163-165).

Nautisitis has studied the reduction of enones with NaBH$_4$/HOAc, conditions which give 1,2-reduction (equations 101-102) (166).

11. GRIBBLE  Sodium Borohydride and Carboxylic Acids

During our studies on the chemoselective reduction of aldehydes, we reported the reduction of the ketoaldehyde shown in equation 103 with $n$-Bu$_4$NBH(OAc)$_3$ and postulated an intramolecular hydride delivery as illustrated (159).

During our studies, Saksena reported the same reaction of NaBH(OAc)$_3$ with $\beta$-hydroxyketones in steroidal systems (167). In particular, he observed excellent stereoselectivities of this (intramolecular) hydride reduction. Subsequently, Evans developed this novel reduction into an extraordinarily useful stereoselective reduction method of $\beta$-hydroxyketones (168, 57), and he fully characterized several of the MBH(OAc)$_3$ reagents for the first time. Examples of this reduction procedure are listed in equations 104-110 (168-174).

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**Equations:**

101: $\text{CHO} \xrightarrow{\text{NaBH}_3\text{OAc} \ (32\% \text{ yield)}} \text{OH} + \text{CHO}$

102: $\text{RC}O \xrightarrow{\text{NaBH}_3\text{OAc} \ (70\% \text{ yield)}} \text{OH} + \text{RCH} = \text{CHO}$

103: $\text{CHO} \xrightarrow{\text{AcO}SO_3\text{H}} \text{OH}$

104: $\text{O}H \xrightarrow{\text{Me}_4\text{NBH(OAc)}_3 \ (92\% \text{ at } -20^\circ\text{C})} \text{OH}$

105: $\text{MeO} \xrightarrow{\text{OTIPS} \ (93\% \text{ at } -40^\circ\text{C})} \text{OH}$

106: $\text{N} \xrightarrow{\text{Me}_4\text{NBH(OAc)}_3 \ (81\% \text{ at } \text{rt})} \text{OH}$
Numerous other examples of this stereoselective β-hydroxyketone reduction have been described in recent years (175-193), including the use of MBH(OAc)₃ in syntheses or synthetic approaches to verrucosidin (194), phorbol (195), streprenol B (196), calycin A (197), lepidicin (198), muamvatin (199), miltiaxone (200), rizoxin (201, 202), myo-inositol derivatives (203), discodermolide (204), acutaphycin (205), and FK-506 (206, 207). Despite the enormous success of this β-hydroxyketone stereoselective reduction, Me₄NBH(OAc)₃ showed no improvement over conventional methods in at least one case (208).

Interestingly, several examples of apparent stereoselective hydroxyl-mediated reductions of α-hydroxyketones have been reported (equations 111-113) (209-211).

Other notable examples of the stereoselective reduction of α-hydroxyketones with MBH(OAc)₃ include the final step in the total syntheses of roaglamide (212, 213) and pancrecine (214).

Conclusions.

Over the past 20 years, the combination of NaBH₄ and RCO₂H has developed into an amazingly versatile and efficient set of reducing and amine alkylating agents. These acylxyborohydride species have rapidly emerged as the preeminent reagents of choice for many chemical transformations. The rapidity to control chemoselectivity, regioselectivity, and stereoselectivity by adjusting the carboxylic acid, hydride reagent, stoichiometry, solvent, temperature and time has no parallel in the arsenal of chemical reagents available to the organic chemist. Nevertheless, despite the extraordinary scope of acyloborohydrides in organic transformations, much work remains to be done in understanding the mechanisms of some of the reactions, such as N-alkylation, and in applying these reagents to asymmetric synthesis.

References

11. Gribble  Sodium Borohydride and Carboxylic Acids


