SODIUM BOROHYDRIDE IN CARBOXYLIC ACID MEDIA.

A REVIEW OF THE SYNTHETIC UTILITY OF ACYLOXYBOROHYDRIDES

Gordon W. Gribble* and Charles F. Nutaitis
Department of Chemistry, Dartmouth College
Hanover, New Hampshire 03755

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INTRODUCTION

Sodium borohydride (NaBH₄), alone or in conjunction with certain metals or solid supports, is one of the most useful reagents in chemistry.¹ Modified versions of NaBH₄, such as sodium cyanoborohydride (NaBH₃CN), also have widespread utility in synthesis.² A relatively new modified-NaBH₄ reagent is that produced when NaBH₄ is allowed to react with a carboxylic acid (RCO₂H) (Eq. 1). The resulting sodium acyloxyborohydrides and their use in organic synthesis are the subject of this review.³

NaBH₄ + x RCO₂H → NaBH₄-x[OCOR]ₓ + xH₂ (1)  

x = 1-3

Unlike the reaction of NaBH₄ with mineral acids or aqueous acids,⁴ which leads to diborane formation or complete hydrolysis, the reaction of NaBH₄ with neat carboxylic acids (RCO₂H) or solutions of RCO₂H in nonprotic solvents leads to the formation of acyloxyborohydrides. Depending on the relative concentration of RCO₂H, one, two, or three hydrides will be available for reaction. Indeed, as will be seen, even in the presence of excess RCO₂H the triacyloxyborohydride species (x = 3, Eq. 1) is relatively stable and only surrenders its
last hydride upon heating or prolonged exposure to RCO₂H. However, all three types of acyloxyborohydrides are rapidly hydrolyzed by water (Eq. 2).

\[
\text{H-O-C-R} \rightarrow \text{H-} + \text{H}_2 + \text{RCO}_2\text{H}
\]  

(2)

As will be apparent in this review, the fact that one can in principle control the number and kind of acyloxy groups on the boron atom leads to remarkable chemoselectivity. The data thus far accumulated indicate the following order of decreasing hydride-donating ability.

\[
\text{BH}_3\text{OCR} > \text{BH}_2(\text{OCR})_2 > \text{BH}(\text{OCR})_3
\]

This reactivity order is presumably a consequence of both the inductive electron-withdrawing ability of the acyloxy group (e.g., \(\sigma_1 = 0.39\) for QAc)⁵ which strengthens the B-H bond and the steric bulk surrounding the B-H bond.

I. HISTORICAL. DISCOVERY AND CHARACTERIZATION OF ACYLOXYBOROHYDRIDES

Interestingly, the first reported synthesis of an acyloxyborohydride, in 1955, did not involve carboxylic acids. Wartik and Pearson⁶ prepared sodium triformyloxyborohydride by allowing NaBH₄ to react with carbon dioxide in dimethyl ether at room temperature (Eq. 3).

\[
\text{NaBH}_4 + 3\text{CO}_2 \xrightarrow{25^\circ} \text{Me}_2\text{O} \xrightarrow{25^\circ} \text{NaBH(OCH)}_3
\]  

(3)
These workers noted that NaBH(OCHO)_3 reacts rapidly with dilute aqueous acid to give dihydrogen, formic acid, and boric acid in the expected stoichiometry. Moreover, they made the important observation that NaBH(OCHO)_3 decomposes on standing, or more rapidly on melting, to give methyl formate. This result implicates the formation of methanol by the self-reduction of NaBH(OCHO)_3 to formaldehyde, thence to methanol, and finally to methyl formate; the ramifications of this observation will be seen later.

At about the same time, Nenitzescu and Badea\(^7\) reported the synthesis of NaBH(OAc)_3, as "a white solid, insoluble in organic solvents," from the reaction of B(OAc)_3 and sodium hydride in boiling dioxane (Eq. 4). A small amount of NaBH(OAc)_2 was reported to be present in the filtrate from which NaBH(OAc)_3 precipitated. These workers also noted that NaBH(OAc)_3 decomposes in moist air and in water. Two years later Reetz\(^8\) and Brown and Subba Rao\(^9\)

\[
\text{NaH} + \text{B(OAc)}_3 \xrightarrow{\text{dioxane}} \text{NaBH(OAc)}_3 \quad (4)
\]

independently described the formation of acyloxyborohydrides from the reaction of NaBH\(_4\) with RCO\(_2\)H (Eqs. 5 and 6).

Reetz\(^8\) isolated NaBH\(_3\)OAc from NaBH\(_4\) and acetic acid in tetrahydrofuran (THF) (Eq. 5), and provided some analytical data in support of the structure. Thus, on reaction with water this substance liberates three moles of dihydrogen. Moreover, no diborane can be detected on heating NaBH\(_3\)O\(_2\)CO\(_2\)CH\(_3\) at 55° for 10 min, although it does react with trialkylphosphites to form (RO)_3PBH\(_3\) in good yield.
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\[ \text{NaBH}_4 + \text{HOAc} \xrightarrow{2. \text{30-40}^\circ} \text{NaBH}_3\text{OAc} + \text{H}_2 \] \hspace{1cm} (5)

Brown and Subba Rao\(^9\) proposed the formation of the related propionic acid derivative (Eq. 6) but no experimental evidence was advanced to support its structure. They also suggested that the reaction of diborane with sodium propionate led to the same material.

\[ \text{CH}_3\text{CH}_2\text{CO}_2\text{H} \xrightarrow{\text{diglyme}} \text{H}_2 + \text{NaBH}_3\text{OCOCH}_2\text{CH}_3 \xrightarrow{\text{D,H}_2\text{6}} \text{CH}_3\text{CH}_2\text{CO}_2\text{Na} \] \hspace{1cm} (6)

Several years later, we\(^10,11\) and Marchini et al.\(^12\) observed that NaBH\(_4\) reacts with excess glacial acetic acid to liberate 3 moles of dihydrogen (Eq. 7). The last hydride is released slowly at 20\(^\circ\) or more rapidly on heating or in the presence of water.

\[ \text{NaBH}_4 + \text{CH}_3\text{CO}_2\text{H} \xrightarrow{20^\circ} 3\text{H}_2 + \text{NaBH(OAc)}_3 \xrightarrow{80^\circ} \text{H}_2 + \text{NaB(OAc)}_4 \] \hspace{1cm} (7)

Marchini and coworkers\(^12\) also reported the preparation and chemical, physical, and spectral properties of several acyloxyborohydrides (Table 1), prepared according to Eq. 8;

\[ \text{NaBH}_4 + 3\text{RCO}_2\text{H} \xrightarrow{200^\circ} \text{NaBH(O}_2\text{CR})_3 + 3\text{H}_2 \] \hspace{1cm} (8)

they also observed that NaBH(OCOC\(_6\text{H}_5\))\(_3\) undergoes self-reduction in refluxing toluene to give benzyl alcohol.

Another Italian group\(^13\) prepared sodium tris(trifluoroacetoxy)borohydride (Eq. 9) and observed a mp of 64-66\(^\circ\) and bands at 1775 and 1680 cm\(^{-1}\) in the infrared spectrum.

\[ \text{NaBH}_4 + 3\text{CF}_3\text{CO}_2\text{H} \xrightarrow{\text{toluene}} \text{NaBH(OCOCF}_3)_3 + 3\text{H}_2 \] \hspace{1cm} (9)
TABLE 1. Properties of Sodium Triacyloxyborohydrides

<table>
<thead>
<tr>
<th>Compound</th>
<th>mp (°C)</th>
<th>IR(cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH(OCHO)₃</td>
<td>&gt;300°</td>
<td>2480</td>
</tr>
<tr>
<td>NaBH(OAc)₃</td>
<td>&gt;300°</td>
<td>2480</td>
</tr>
<tr>
<td>NaBH(OCOPh)₃</td>
<td>&gt;300°</td>
<td>2490</td>
</tr>
<tr>
<td>NaBH(OOCCH₂Cl)₃</td>
<td>120–5° (dec)</td>
<td>2530</td>
</tr>
</tbody>
</table>

Egan and Morse⁴ have recorded the IR spectrum of NaBH₂OAc and observed 2500 and 1683 cm⁻¹ for the B–H and C=O stretching absorptions, respectively. These workers also noted, as did Hui,¹⁵ that NaBH₂(OAc)₂ could not be prepared cleanly.

However, Hui¹⁵ was able to synthesize the malonic acid-derived acyloxyborohydride shown below, perhaps the only known stable diacyloxyborohydride species.

![Malonic Acid Derivatives](image)

The remaining few cases of acyloxyborohydride isolation and study will be presented in the appropriate section to follow.

In most of the examples of the use of acyloxyborohydrides in synthesis (vide infra), the reagent is not isolated per se but, rather, is generated and utilized in situ. Therefore, in the ensuing discussion we have not specified the actual acyl-
oxyborohydride reagent, except where it has been isolated and employed as such.

Finally, it will be noted that this review covers also NaBH₃CN, LiBH₄, KBH₄, and n-Bu₄NBH₄ in combination with carboxylic acids.

II. REDUCTION OF ENAMINES

Apparently, the first reported use of NaBH₄/RCO₂H in organic synthesis was the reduction of two steroidal di-enamines by Marshall and Johnson¹⁶ (Eq. 10 and 11) and, in fact, was the final step in their total synthesis of (1)-conessine¹⁶c (Eq. 10).

![Diagram](image)

These workers also showed that simple enamines were reduced under these conditions, and since then a number of other enamine reductions have been described (Table 2). Noteworthy is the extensive study by Hutchins¹⁹ (entries 4–7). Sodium cyanoborohydride can be substituted for NaBH₄.
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(entries 3, 6, 8), especially if amine alkylation is to be avoided (vide infra).

From these studies it is clear that reductions of enamines (via immonium ions) with sodium triacetoxysorohydride are reasonably (entries 2, 4-6) to highly (entry 7) stereoselective, with the preferred approach being from the less hindered side (equatorial attack) to give the axial product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![substrate image]</td>
<td>![product image]</td>
<td>NaBH₄, THF, HOAc, A, 1 hr</td>
<td>70%</td>
<td>16a</td>
</tr>
<tr>
<td>2</td>
<td>![substrate image]</td>
<td>![product image]</td>
<td>NaBH₄, THF, HOAc, rt</td>
<td>80%</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(major)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>![substrate image]</td>
<td>![product image]</td>
<td>NaBH₄CN, MeCN, HOAc, rt, 10 min</td>
<td>78%</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>![substrate image]</td>
<td>![product image]</td>
<td>NaBH₄, HOAc, 25°, 24 hr</td>
<td>72% : 28 / 325</td>
<td>19</td>
</tr>
</tbody>
</table>
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\[
\begin{align*}
5 & \quad \text{C(CH}_3\text{)}_3 \quad \text{C(CH}_3\text{)}_3 \\
& \quad 79 : 21 \\
& \quad \text{NaBH}_4 \quad \text{HOAc} \\
& \quad 25^\circ, 24 \text{ hr} \\
6 & \quad \text{89} : 11 \\
& \quad \text{NaBH}_3\text{CN} \quad \text{HOAc} \\
& \quad 25^\circ, 24 \text{ hr} \\
7 & \quad \text{98} : 2 \\
& \quad \text{NaBH}_4 \quad \text{HOAc} \\
& \quad 25^\circ, 24 \text{ hr} \\
8 & \quad \text{NaBH}_3\text{CN} \quad \text{HOAc, MeCN} \\
& \quad 75\% 20 \\
& \quad 2:1 \text{ cis/trans}
\end{align*}
\]

III. REDUCTION OF VINYLLOGOUS AMIDES, CARBAMATES, UREAS AND N-ACYLENAMINES

Another pioneering application of NaBH₄/RCO₂H methodology was the chemoselective reduction of the vinyllogous carbamate double bond in vallesia chotamine as reported in 1966 by Djerassi²¹ (Eq. 12). The aldehyde functionality was also reduced, but, interestingly, the indole double bond was not reduced, in contrast to studies discussed later (Section V).
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\[
\begin{align*}
\text{CHO} & \quad \text{CO}_2\text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CO}_2\text{CH}_3 \\
\text{CHO} & \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{CO}_2\text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{CO}_2\text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{CO}_2\text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Several other examples of this particular reduction have been revealed (Table 3). Noteworthy is the fact that the stronger trifluoroacetic acid can be used (entry 3) and that acyclic systems may undergo \(\beta\)-elimination (entry 4).

**TABLE 3. Reduction of Vinylogous Amides, Carbamates, Ureas and N-Acyl enamines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>NaBH₄</td>
<td>80%</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc, 0°C → rt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>NaBH₃CN</td>
<td>75%</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc, THF, MeOH, 45°C, 4 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>NaBH₄</td>
<td>55%</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CF₃CO₂H, PhH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>NaBH₄</td>
<td>60-80%</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CF₃CO₂H, i-ProH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R₁ = i-Pr, Ph, C₆H₁₃
R₂ = i-bu, Pr, neo-pentyl
R₃ = Et, -CH₂CH₂OCH₂CH₂⁻
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IV. REDUCTION OF IMINES, IMMONIUM SALTS, AND RELATED SYSTEMS

In view of the results described in the previous two sections, it is not surprising that imines and immonium salts are smoothly reduced to amines (Table 4). Depending on the system and reaction conditions, the initially-produced amine may be N-alkylated by the carboxylic acid (entries 2, 3, 13). This novel amine alkylation will be discussed in detail in Section VI. The NaBH₄/RCO₂H reduction of imines is analogous to that utilizing NaBH₃CN/MeOH/pH 3.²⁷ Several points about Table 4 should be made. Pyridine, pyrimidine, and furan rings (entries 3, 5, 15, 16) are generally inert to the action of NaBH₄ (or NaBH₃CN)/RCO₂H. In some cases very useful ring cleavage is observed (entries 7, 8, 12) and Wasserman has made extensive use of this reductive cleavage in his elegant syntheses of spermine/spermidine alkaloids.²⁶,³² The N-trifluoroethyla-
tion (entry 13) can be suppressed by using NaBH₃CN/CF₃CO₂H. It is interesting to note that the acetic acid-induced ring opening observed by Sakai³⁴ (entry 12) is not observed when trifluoroacetic acid is used (entry 13). Especially noteworthy is the high degree of asymmetric reduction observed with a NaBH₄/proline acyloxyborohydride complex (entries 9, 10). Several other imines and optically active amino acids were examined in this important study.³³ Finally, Weinreb has used this methodology (NaBH₃CN/CF₃CO₂H) to effect a
convenient N-methylation of primary and secondary amides (entries 14-16), in a transformation that presumably involves the formation and subsequent reduction of acylimmonium ion intermediates (cf. Table 3, entry 5 for a related example).

**TABLE 4. Reduction of Imines, Immonium Salts, and Related Systems**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image2" alt="Structure 2" /></td>
<td>NaBH₄ (1 eq.), CH₃CO₂H, 80°C, 1 hr</td>
<td>60-95% 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="image3" alt="Structure 3" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="image4" alt="Structure 4" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="image5" alt="Structure 5" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a; R₁ = R₂ = Me, R₃ = Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b; R₁ = H, R₂ = R₃ = Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image6" alt="Structure 6" /></td>
<td><img src="image7" alt="Structure 7" /></td>
<td>NaBH₄ (5 eq.), HOAc, 80°C, 3 hr</td>
<td>75-95% 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="image8" alt="Structure 8" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="image9" alt="Structure 9" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a; R₁ = R₂ = Me, R₃ = Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b; R₁ = H, R₂ = R₃ = -(CH₂)₅⁻</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image10" alt="Structure 10" /></td>
<td><img src="image11" alt="Structure 11" /></td>
<td>NaBH₄, HCO₂H, 10°C-25°C</td>
<td>84% 28</td>
</tr>
<tr>
<td></td>
<td>(others)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image12" alt="Structure 12" /></td>
<td><img src="image13" alt="Structure 13" /></td>
<td>NaBH₃CN, HOAc, rt</td>
<td>95% 29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image14" alt="Structure 14" /></td>
<td><img src="image15" alt="Structure 15" /></td>
<td>NaBH₄, CF₃CO₂H, rt</td>
<td>51% 30</td>
</tr>
</tbody>
</table>

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6. MeO\(\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \) CO\(_2\text{Et}\) MeO\(\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \) CO\(_2\text{Et}\)

\[
\text{NaBH}_3\text{CN} \quad 94\% \quad 31 \\
\text{HOAc} \\
\text{rt, 3 hr;} \\
50^\circ, 1 \text{ hr}
\]

7. Ph\(\text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph}\)

\[
\text{NaBH}_3\text{CN} \quad 88\% \quad 32 \\
\text{HOAc}
\]

8. Ph\(\text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph}\)

\[
\text{NaBH}_3\text{CN} \quad 93\% \quad 26,32 \\
\text{HOAc} \\
25^\circ, 3 \text{ hr} \\
50^\circ, 1 \text{ hr}
\]

9. MeO\(\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \) 60% ee

\[
\text{NaBH}_4 \quad 68\% \quad 33 \\
\text{THF}
\]

10. \(\text{H} \quad \text{H} \quad \text{H} \quad \text{H}\) CH\(_3\)

\[
\text{NaBH}_4 \quad 85\% \quad 33 \\
\text{THF} \\
79\% \text{ ee}
\]

11. MeO\(\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \) OMe\(\text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}\)

\[
\text{NaBH}_4 \quad 77\% \quad 34 \\
\text{HOAc}
\]
V. REDUCTION OF INDOLES

Our own research in the area of NaBH₄/RCO₂H methodology began in 1973 when the senior author attempted to reduce indole to indoline with NaBH₄ in glacial acetic acid. Much to our surprise, the product was not indoline but rather N-ethyl-indoline in 86% distilled yield (Eq. 13).
Control experiments and other data show that indoline is formed rapidly and then undergoes N-alkylation to give product. Details of this N-alkylation will be described in Section VI. This synthesis of N-alkylindolines is general for a variety of indoles and carboxylic acids (Eq. 14).

By using NaBH₃CN in place of NaBH₄, one can avoid N-alkylation and achieve a very simple and efficient synthesis of indolines (Eq. 15). Only those indoles having electron-withdrawing groups fail to undergo reduction (e.g., 5-nitro- and 2,3-diphenylindole); this modification using NaBH₃CN/HOAc to reduce indoles to indolines was recently "rediscovered" by Kumar and Florvall.

\[
\begin{align*}
\text{R}_2, \text{R}_3 &= \text{H, Me, -}(\text{CH}_2)_4^- \\
\text{R}_1 &= \text{H, Me, Et, i-Pr} \\
\text{R}_4 &= \text{H, 5-Br, 7-Me}
\end{align*}
\]
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It is important to note that earlier workers did not observe reduction of the indole double bond because in these systems (e.g. Eq. 12; Table 3, entries 1, 2; Table 4, entry 12) a basic nitrogen atom is present which, when protonated, protects the indole ring from protonation and reduction. However, as can be seen in Table 5, the stronger trifluoroacetic acid overcomes this difficulty and reduction of the indole double bond can be achieved.

Several additional examples of the use of NaBH₄ (or NaBH₃CN)/ RCO₂H to reduce the indole ring are tabulated in Table 5. A striking example of the inherent chemoselectivity noted earlier is seen in the reduction of only the more basic indole double bond in the molecule shown in entry 3.

Generally, the use of trifluoroacetic acid does not give much N-trifluoroethylolation; however, if this becomes a problem (entry 6), then NaBH₃CN can be substituted for NaBH₄. Alternatively, lesser amounts of NaBH₄ (or KBH₄) may be used (entry 8).

As discussed in Section II, the reduction can be highly stereoselective giving product resulting from axial protonation and hydride delivery from an equatorial direction (entries 4, 5, 8). However, in simple indole systems there is virtually no stereoselectivity (entries 9, 10).

Indole itself undergoes an interesting reaction with NaBH₄/CF₃CO₂H, which will be discussed in Section XIX.
**TABLE 5. Reduction of Indoles**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 1" /></td>
<td><img src="image" alt="Product 1" /></td>
<td>NaBH$_3$CN, HOAc, rt</td>
<td>86%</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 2" /></td>
<td><img src="image" alt="Product 2" /></td>
<td>NaBH$_4$, HOAc, rt, 30 min</td>
<td>100%</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 3" /></td>
<td><img src="image" alt="Product 3" /></td>
<td>NaBH$_3$CN, HOAc, rt</td>
<td>78%</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 4" /></td>
<td><img src="image" alt="Product 4" /></td>
<td>NaBH$_4$, CF$_3$CO$_2$H, 0°C</td>
<td>90%</td>
<td>11, 43</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Substrate 5" /></td>
<td><img src="image" alt="Product 5" /></td>
<td>NaBH$_3$CN, MeOH, CF$_3$CO$_2$H</td>
<td>82%</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Substrate 6" /></td>
<td><img src="image" alt="Product 6" /></td>
<td>NaBH$_3$CN, CF$_3$CO$_2$H, (NaBH$_4$, CF$_3$CO$_2$H)</td>
<td>81%</td>
<td>45</td>
</tr>
</tbody>
</table>

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7

\[
\begin{aligned}
\text{NaBH}_4 &\quad 67\% \quad 46 \\
\text{CF}_3\text{CO}_2\text{H} &\quad 0^\circ \quad \text{to} \quad 10^\circ \\
\end{aligned}
\]

8

\[
\begin{aligned}
R = \text{Me, Cl, F, Br, CO}_2\text{Et} &\quad 1-2 \text{ moles} \quad 80\% \quad 47 \\
\text{KBH}_4 &\quad (\text{or NaBH}_4) \\
\text{CF}_3\text{CO}_2\text{H} &
\end{aligned}
\]

9

\[
\begin{aligned}
\text{NaBH}_4 &\quad >95\% \quad 48 \\
\text{CF}_3\text{CO}_2\text{H} &\quad (\text{gc}) \\
60:40 &\quad \text{trans/cis}
\end{aligned}
\]

10

\[
\begin{aligned}
\text{NaBH}_3\text{CN} &\quad 84\% \quad 49 \\
\text{CF}_3\text{CO}_2\text{H} &\\
56:44 &\quad \text{trans/cis}
\end{aligned}
\]

11

\[
\begin{aligned}
\text{NaBH}_4 &\quad 80-100\% \quad 35,50 \\
\text{or NaBH}_3\text{CN} &\quad \text{CF}_3\text{CO}_2\text{H}
\end{aligned}
\]

The reaction of 3-acylindoles with NaBH_4/RCO_2H can take a complicated course (Eq. 16^{51} and 17^{41}).

\[
\begin{aligned}
\text{indole} &\quad \text{CH}_3 \\
\overset{\text{NaBH}_4}{\text{HOAc}} &\quad 60^\circ \\
50\% &\quad \text{Et} \\
\text{Et} &\quad 31\% \\
\end{aligned}
\]
Likewise, the reaction of indole with NaBH₄/HCO₂H gives, in addition to the expected N-methylindoline (Eq. 14),¹¹ the dimeric product shown in Eq. 18.⁵² This aberrant pathway has not been observed with other carboxylic acids.

VI. N-ALKYLATION OF AMINES

Perhaps the most extraordinary property of the NaBH₄/-RCO₂H reagent is its ability to N-alkylate amines, alluded to several times earlier. We believe that the mechanism for this transformation involves self-reduction of the acyloxyborylhydride species to give free aldehyde (or its synthetic equivalent) followed by condensation with the amine and reduction to the N-alkylated amine.¹¹

The power and versatility of this amine alkylation methodology is illustrated in Eq. 19.¹¹,⁵¹
Thus, one can prepare unsymmetrical tertiary amines from primary amines in one pot, introduce the very bulky neopentyl group using pivalic acid, control the reaction (in some cases) so as to stop at the secondary amine stage, and use ketones so as to introduce secondary alkyl groups.

Simultaneously and independently of our own work, Marchini and coworkers also discovered this amine N-alkylation and extended it to the use of solid carboxylic acids in cosolvents. This important contribution as well as other examples of this amine N-alkylation are tabulated in Tables 6 (aromatic amines) and 7 (aliphatic amines).
The \textit{N}-alkylation of aromatic amines works equally well for nonbasic amines (entries 6-9), can be made chemoselective in the presence of an aliphatic amine (which requires higher temperatures for \textit{N}-alkylation, cf., Table 7) (entries 10, 11, 23), and can be controlled so as to give mono- or dialkylolation (entries 10-14). Moreover, a variety of functional groups (hydroxyl, alkene, carboxethoxy, sulfur, amide, aryl ketone) and heterocyclic rings (pyridine, thiophene, thiadiazole) are unaffected by the appropriate \( \text{NaBH}_4/\text{RCO}_2\text{H} \) conditions. In contrast to other carboxylic acids, trifluoroacetic acid gives lower yields of \textit{N}-trifluoroethylolation in most cases (entries 21-25).

\section*{TABLE 6. \textit{N}-Alkylation of Aromatic Amines}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield Ref.</th>
</tr>
</thead>
</table>
| 1     | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{H, Me, Et}
\end{align*} | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{H, Me, Et}
\end{align*} | \begin{align*} & \text{NaBH}_4 \\
& \text{RCO}_2\text{H} \\
& \text{Toluene} \\
& \Delta 
\end{align*} | 72-83\% 11 |
| 2     | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{Me, Et}
\end{align*} | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{Me, Et}
\end{align*} | \begin{align*} & \text{NaBH}_4 \\
& \text{RCO}_2\text{H} \\
& \text{Toluene} \\
& \Delta 
\end{align*} | 90\% 12 |
| 3     | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{H, Me, Et}
\end{align*} | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{H, Me, Et}
\end{align*} | \begin{align*} & \text{NaBH}_4 \\
& \text{HOAc} \\
& \text{50-60\degree}
\end{align*} | 88\% 11 |
| 4     | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{H, Me, Et}
\end{align*} | \begin{align*} & \text{\textit{N}-H} \\
& \text{CH}_2\text{R} \\
& \text{R} = \text{H, Me, Et}
\end{align*} | \begin{align*} & \text{NaBH}_4 \\
& \text{RCO}_2\text{H} \\
& \text{THF}
\end{align*} | 68-83\% 53 |
SODIUM BOROHYDRIDE IN CARBOXYLIC ACID MEDIA. A REVIEW

5 \[ \text{reaction scheme} \]

6 \[ \text{reaction scheme} \]

7 \[ \text{reaction scheme} \]

8 \[ \text{reaction scheme} \]

9 \[ \text{reaction scheme} \]

10 \[ \text{reaction scheme} \]

11 \[ \text{reaction scheme} \]

12 \[ \text{reaction scheme} \]

13 \[ \text{reaction scheme} \]

14 \[ \text{reaction scheme} \]

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<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td><img src="image1" alt="Image" /></td>
<td>NaBH$_4$ CF$_3$CO$_2$H</td>
<td>7% 11,59</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td><img src="image2" alt="Image" /></td>
<td>NaBH$_4$ CF$_3$CO$_2$H</td>
<td>61% 59</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td><img src="image3" alt="Image" /></td>
<td>KBH$_4$ CF$_3$CO$_2$H</td>
<td>89% 47</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td><img src="image4" alt="Image" /></td>
<td>NaBH$_4$ CF$_3$CO$_2$H toluene</td>
<td>64% 13</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td><img src="image5" alt="Image" /></td>
<td>NaBH$_4$ CF$_3$CO$_2$H 20°, 4 hr</td>
<td>25% 13</td>
<td></td>
</tr>
</tbody>
</table>

The N-alkylation of aliphatic amines using NaBH$_4$/RCO$_2$H is tabulated in Table 7. It has proven to be a very general method with both primary and secondary amines and a variety of carboxylic acids (neat or in a cosolvent such as benzene). Hinderned amines alkylate poorly (entries 8-10) or not at all (entry 28). The use of a ketone allows for the introduction of a secondary alkyl group (entry 13) or for the introduction of two different alkyl groups in converting a primary amine to a tertiary amine (entry 14). In some cases one can achieve N-monoalkylation of a primary amine (entries 15, 21).
The Marchini modification using benzene as a cosolvent has been widely used (entries 17–27) by three groups to synthesize an array of dopamine analogues.

Fewer examples of N-methylation of aliphatic amines using NaBH₄/HCO₂H have been reported (Table 6, entry 20), perhaps because alternative, well-established methods exist (e.g., HCHO/NaBH₃CN) and the reaction of NaBH₄ with neat formic acid is exceptionally vigorous and unpleasant to conduct.

### TABLE 7. N-Alkylation of Aliphatic Amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{CH}_2\text{NHR} )</td>
<td>( \text{CH}_2\text{R'} )</td>
<td>NaBH₄, R\text{'CO}_2\text{H} ( 50-55^\circ )</td>
<td>62-84%</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>( R = \text{Me, Et, CH}_2\text{Ph, i-Pr, t-Bu} )</td>
<td>( R' = \text{Me, Et, n-Pr, i-Pr, t-Bu} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>( \text{N} )</td>
<td>( \text{CH}_2\text{CH}_3 )</td>
<td>NaBH₄, HOAc ( 50-55^\circ )</td>
<td>74%</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>( \text{N} )</td>
<td>( \text{CH}_2\text{CH}_3 )</td>
<td>NaBH₄, HOAc ( 50-55^\circ )</td>
<td>69-84%</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>( X = \text{CH}_2, \text{O, NMe} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>( \text{CH}_3\text{NH}_2\text{Cl} )</td>
<td>( \text{CH}_3\text{CH}_2\text{N(CH}_2\text{)}_8\text{CH}_3 )</td>
<td>NaBH₄, CH₃(CH₂)₇CO₂H, THF</td>
<td>78%</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NAOAC, ( 50-55^\circ )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>( \text{CH}_3\text{CH}_2\text{NH} )</td>
<td>( \text{CH}_3\text{CH}_2\text{N(CH}_2\text{)}_7\text{CH}_3 )</td>
<td>NaBH₄, CH₃(CH₂)₆CO₂H ( 50-55^\circ )</td>
<td>70%</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>( \text{N} )</td>
<td>( \text{CH}_2\text{NCH}_2\text{R} )</td>
<td>NaBH₄, ( \text{RCO}_2\text{H} )</td>
<td>58-65%</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>( R = \text{Me, Et} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>#</th>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>nBu₂NH</td>
<td>nBu₂NEt</td>
<td>NaBH₄, HOAc, 80°, 3 hr</td>
<td>80%</td>
<td>12 hr</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>NaBH₄, HOAc, 50-55°</td>
<td>14%</td>
<td>60 min</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>NaBH₄, HOAc, 50-55°</td>
<td>13%</td>
<td>60 min</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>NaBH₄, HOAc, 50-55°</td>
<td>9%</td>
<td>60 min</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>NaBH₄, i-Pr-CO₂H</td>
<td>90%</td>
<td>51 min</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>NaBH₄, HOAc, 50-55°</td>
<td>66%</td>
<td>60 min</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td>NaBH₄, HOAc, 25°</td>
<td>84%</td>
<td>60 min</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td>NaBH₄, HOAc, 25°</td>
<td>82%</td>
<td>60 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. 50-55°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td>NaBH₄, HOAc, 45°, 4 hr</td>
<td>61%</td>
<td>51 min</td>
</tr>
<tr>
<td>16</td>
<td>(CH₃)₂NH</td>
<td>(CH₃)₂N(CH₂)₁₂N(CH₃)₂</td>
<td>NaBH₄, HO₂C(CH₂)₁₀CO₂H</td>
<td>21%</td>
<td>61 hr</td>
</tr>
<tr>
<td>17</td>
<td>MeO-[NH₂]</td>
<td>MeO-[N(CH₂)₂Ph]₂</td>
<td>NaBH₄, PhCH₂CO₂H, PhH, Δ</td>
<td>51%</td>
<td>62 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>Δ</td>
<td>19 hr</td>
</tr>
</tbody>
</table>
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18. \[
\begin{align*}
\text{MeO-} & \quad \text{MeO-} \\
\text{NH}_{2}\text{Bu} & \quad \text{N-dBu} \\
R = \text{Et, n-Pr} & \quad \text{RCO}_{2}\text{H} \\
& \quad \text{PhH} \\
& \quad \Delta \\
& \quad 3 \text{ hr}
\end{align*}
\]
\[
\text{NaBH}_4 \quad 80-86\% \quad 62
\]

19. \[
\begin{align*}
\text{CO}_2\text{CH}_3 & \\
\text{NH} & \\
\text{EtCO}_2\text{H} & \\
& \quad \text{PhH} \\
& \quad \Delta
\end{align*}
\]
\[
\text{NaBH}_4 \quad 72\% \quad 63
\]

(15 molar 54-87\% 64 equiv.)

20. \[
\begin{align*}
\text{MeO-} & \quad \text{MeO-} \\
\text{NH}_2 & \quad \text{NICH}_2\text{R}_2 \\
R = \text{Me, Et, n-Pr} & \quad \text{RCO}_2\text{H} \\
& \quad \text{PhH} \\
& \quad \Delta, 16 \text{ hr}
\end{align*}
\]
\[
\text{NaBH}_4 \quad 53-75\% \quad 66
\]

(2 molar 38\% 64 equiv.)

21. \[
\begin{align*}
\text{MeO-} & \quad \text{MeO-} \\
\text{NH}_{2}\text{Pr} & \quad \text{NH}_{2}\text{Pr} \\
\text{EtCO}_2\text{H} & \\
& \quad \text{PhH} \\
& \quad \Delta
\end{align*}
\]
\[
\text{NaBH}_4 \quad 96\% \quad 65
\]

22. \[
\begin{align*}
\text{MeO-} & \quad \text{MeO-} \\
\text{NH}_2\text{Et} & \quad \text{NMe}_2 \\
\text{HOAc} & \\
& \quad \text{PhH} \\
& \quad \Delta
\end{align*}
\]
\[
\text{NaBH}_4 \quad 43\% \quad 67
\]

23. \[
\begin{align*}
\text{MeO-} & \quad \text{MeO-} \\
\text{NH}_2 & \quad \text{N(CH}_2\text{R}_2 \\
R = \text{Me, Et} & \quad \text{RCO}_2\text{H} \\
& \quad \text{PhH} \\
& \quad 20 \text{ hr, } \Delta
\end{align*}
\]

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VII. REDUCTION AND REDUCTION/\textit{N}-ALKYLATION OF \textit{\gamma}-DEFICIENT HETEROCYCLES

Following an early report by Rao and Jackman\textsuperscript{73} on the reduction of nitroquinolines and related compounds with \(\text{NaBH}_4/\text{HOAc}\), numerous examples of the reduction of \textit{\gamma}-deficient
heterocycles using this methodology have been disclosed (Table 8). As has been seen earlier, the reaction can be controlled by changing either the borohydride reagent or the temperature to give reduction with or without N-alkylation (entries 1 and 3, 2 and 5, 9 and 10, 14 and 16, 19 and 20, 24 and 25). A ketone can be employed to give a secondary N-alkyl group (entry 6). Only in the case of nitroquinolines does the reduction stop at the 1,2-dihydroquinoline stage (entries 9, 10), although, in the presence of acetic anhydride, the 1,2-dihydro heterocycles can be trapped in the case of quinoline and isoquinoline (entries 12-13). The reduction of quinoline and isoquinoline with NaBH₄/CF₃CO₂H (not shown in Table 8) gives a mixture of the corresponding 1,2,3,4-tetrahydro heterocycle and the N-trifluoroethylated derivative (17-21%).

Although pyridine is not reduced with NaBH₄/RCO₂H, under conditions thus far investigated,⁵¹ pyridines containing 3,5-electron-withdrawing groups are smoothly reduced to the 1,4-dihydro compounds with NaBH₃CN/HOAc (entries 27-29) but not with NaBH₄/HOAc (entry 26).

**TABLE 8. Reduction and Reduction/N-Alkylation of τ-Deficient Heterocycles**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td>NaBH₃CN HOAc⁷ 50°, 1 hr</td>
<td>71% 53</td>
</tr>
</tbody>
</table>

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2  \begin{align*}
\text{NaBH}_3\text{CN} & \quad 71\% \ 53 \\
\text{HOAc} & \quad 50^\circ, \ 1 \ hr
\end{align*}

3  \begin{align*}
\text{NaBH}_4 & \quad 52-68\% \ 53 \\
\text{RCOO}_2\text{H} & \quad 50^\circ
\end{align*}
\[ R = \text{H, Me, Et} \]

4  \begin{align*}
\text{NaBH}_4 & \quad 65\% \ 53 \\
\text{HOAc} & \quad 50^\circ, \ 2.5 \ hr
\end{align*}

5  \begin{align*}
\text{NaBH}_4 & \quad 76-79\% \ 53 \\
\text{RCOO}_2\text{H} & \quad 50^\circ
\end{align*}
\[ R = \text{H, Me, Et} \]

6  \begin{align*}
\text{NaBH}_4 & \quad 59\% \ 53 \\
\text{HOAc} & \quad \text{CH}_3\text{COCH}_3 \\
& \quad 50^\circ, \ 1 \ hr
\end{align*}

7  \begin{align*}
\text{NaBH}_3\text{CN} & \quad 44-66\% \ 74 \\
\text{HOAc} & \quad 55^\circ, \ 1.5 \ hr
\end{align*}
\[ R = \text{H, Me} \]

8  \begin{align*}
\text{NaBH}_4 & \quad 45-68\% \ 75 \\
\text{ClCH}_2\text{CO}_2\text{H} & \quad \text{THF}
\end{align*}
\[ R = \text{H, 6-Me, 5-Cl} \] (2-Me failed)

9  \begin{align*}
\text{NaBH}_4 & \quad 67-90\% \ 73 \\
\text{HOAc} & \quad 5^\circ
\end{align*}
\[ R = 5, \ 6, \ 7, \ 8-\text{NO}_2 \]

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\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{O}_2\text{N} \\
\text{N} & \quad \text{N} \\
\text{CH}_2\text{CH}_3 & \quad \text{CH}_2\text{CH}_3
\end{align*}
\]

NaBH\textsubscript{4} HOAc 44% 53

11

\[
\begin{align*}
\text{NO}_2 & \quad \text{NO}_2 \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H}
\end{align*}
\]

NaBH\textsubscript{4} HOAc 50° 59

12

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

NaBH\textsubscript{4} HOAc Ac\textsubscript{2}O 60°, 2 hr 72% 76

13

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

NaBH\textsubscript{4} HOAc Ac\textsubscript{2}O 60°, 2 hr 80% 76

14

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

NaBH\textsubscript{4} CF\textsubscript{3}CO\textsubscript{2}H THF rt, 1 hr 90% 77

15

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

R = 5-NO\textsubscript{2}, 6-NO\textsubscript{2}, 6-CN, 6-C\textsubscript{2}F\textsubscript{3}, 6-CO\textsubscript{2}Et

NaBH\textsubscript{4} HOAc 43-87% 73

16

\[
\begin{align*}
\text{CH}_2\text{R} & \quad \text{CH}_2\text{R} \\
\text{N} & \quad \text{N}
\end{align*}
\]

KBH\textsubscript{4} RCO\textsubscript{2}H Δ, 6 hr R = H, Me, Et 70-87% 78

17

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{NCH}_2\text{R} & \quad \text{NCH}_2\text{R}
\end{align*}
\]

KBH\textsubscript{4} RCO\textsubscript{2}H Δ, 6 hr R = H, Me, Et 41-97% 78

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18 \[
\text{NaBH}_4 \quad \text{CP}_3\text{CO}_2\text{H} \\
\text{THF} \quad \text{rt, 1 hr}
\]

19 \[
\text{NaBH}_4 \quad 75\% \quad 77
\]

20 \[
\text{KBH}_4 \quad 43-66\% \quad 78
\]

R = H, Me, Et

21 \[
\text{NaBH}_4 \quad 96\% \quad 77
\]

22 \[
\text{NaBH}_4 \quad 58-75\% \quad 79
\]

\[
\text{HOAc} \quad \text{rt, 20 min}
\]

23 \[
\text{NaBH}_4 \quad \text{failed} \quad 79
\]

\[
\text{HOAc} \quad \text{rt, 20 min}
\]

24 \[
\text{NaBH}_4 \quad 96\% \quad 51
\]

\[
\text{HOAc} \quad 20^\circ
\]

25 \[
\text{NaBH}_4 \quad 82\% \quad 51
\]

\[
\text{HOAc} \quad 75^\circ
\]
GRIBBLE AND NUTAITIS

26 RO₂C-      CO₂R RO₂C-      CO₂R RO₂C-      CO₂R
    N             H              N             H            N
R = Me: 60%       40%  R = Et: 62%       38%  NaBH₄  HOAc  57-76% 80

27  RO₂C-      CO₂R
    N
R = H, Me, Et  NaBH₃CN  HOAc  74-77% 80

28  NC-        CN    NC-        CN
    N
NaBH₃CN  HOAc  98% 80

29  EtO₂C-      CO₂EtEtO₂C-      CO₂Et
    Me  Me  Me  Me  NaBH₃CN  HOAc  60% 80

VIII. REDUCTION AND REDUCTION/N-ALKYLATION OF OXIMES

Depending on the reaction conditions, oximes can be reduced either to N-monoalkylhydroxylamines or N,N-dialkylhydroxylamines, and oxime ethers can be reduced to primary amines (Table 9). The unsymmetrical dialkylhydroxylamines so prepared would be very difficult to synthesize other ways.

In some cases, aberrant reaction products are obtained, especially with aldoximes, where the initially-formed monoalkylhydroxylamine condenses with the oxime leading, after reduction, to the symmetrical dialkylhydroxylamine where both alkyl groups derive from the oxime (entry 6). Another side reaction is overreduction and subsequent alkylation, an example of which is shown in Eq. 20.81 Note that this particular reaction also gives a product of the type formed in entry 6.
SODIUM BOROHYDRIDE IN CARBOXYLIC ACID MEDIA. A REVIEW

\[
\text{PhCH-NOH} + \text{NaBH}_4/\text{(CH}_3\text{)_3CO}_2\text{H} \rightarrow \text{PhCH}_2\text{N}^+\text{C}(-\text{CH}_3)_3\text{CH}_2\text{C}(-\text{CH}_3)_3^+ + \text{PhCH}_2\text{N}^+\text{CH}_2\text{Ph}
\]

(20)

**TABLE 9. Reduction and Reduction/N-Alkylation of Oximes, Oxime Ethers, and Oxime Esters**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>NaBH₄</td>
<td>36-87%</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R⁺CO₂H</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40-50°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-5 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = H, Me</td>
<td>R' = Me, Et, t-Bu, Ph, CH₂-Ph, n-Pr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R, R' = -(CH₂)₅⁻</td>
<td>R&quot; = Me, Et, i-Pr, n-Pr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>NaBH₃CN</td>
<td>81%</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(NaBH₄)</td>
<td>(63%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>NaBH₃CN</td>
<td>70-92%</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = CH₂Ph, R' = Me</td>
<td>R, R' = -(CH₂)₅⁻, -(CH₂)₅⁻</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>NaBH₄</td>
<td>81-91%</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CF₃CO₂H</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = Ph, n-C₅H₁₉, CH₂CH₂Ph</td>
<td>R', R&quot; = -(CH₂)₅⁻, -(CH₂)₆⁻</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R' = Me, H, Ph</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>NaBH₄</td>
<td>51%</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CF₃CO₂H</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diglyme</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R, R' = -(CH₂)₅⁻, -(CH₂)₆⁻</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>NaBH₄</td>
<td>21%</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = H, Me</td>
<td>R&quot; = Me, Et, i-Pr, n-Pr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R, R' = -(CH₂)₅⁻</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>351</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GRIBBLE AND NUTAITIS

IX. REDUCTION OF OTHER C=N COMPOUNDS

As might be anticipated from the results in the previous Section, a smattering of other C=N species have been reduced with NaBH$_4$/RCO$_2$H. These are tabulated in Table 10. Noteworthy is the convenient reductive deoxygenation of carbonyl compounds via their tosylhydrazones as developed by Hutchins and Natale$^{85}$ (entries 2-4).

TABLE 10. Reduction of Other C=N Compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate Image" /></td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>NaBH$_4$ HOAc dioxane EtOH rt</td>
<td>76%</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$(CH$_2$)$_4$C(CH$_2$)$_4$CH$_3$</td>
<td>CH$_3$(CH$_2$)$_9$CH$_3$</td>
<td>NaBH$_4$ HOAc 70$^\circ$ 1-2 hr</td>
<td>84%</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Substrate Image" /></td>
<td><img src="image4.png" alt="Product Image" /></td>
<td>NaBH$_4$ HOAc 70$^\circ$ 1-2 hr</td>
<td>72%</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><img src="image5.png" alt="Substrate Image" /></td>
<td><img src="image6.png" alt="Product Image" /></td>
<td>NaBH$_4$ HOAc 70$^\circ$, 1-2 hr</td>
<td>56%</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td><img src="image7.png" alt="Substrate Image" /></td>
<td><img src="image8.png" alt="Product Image" /></td>
<td>NaBH$_3$CN CF$_3$CO$_2$H THF</td>
<td>97%</td>
<td>86</td>
</tr>
</tbody>
</table>
X. REDUCTION OF NITRILES

Although nitriles are not reduced under conditions which produce NaBH(OCOR)_3 (Table 8, entries 15 and 28; Table 15, entry 1), Umino and coworkers^87 have shown that nitriles are smoothly reduced to primary amines with NaBH_3OCOCF_3 (in situ) in THF at rt (Table 11). The reduction is poor with NaBH_3OAc.

Table 11. Reduction of Nitriles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-CN</td>
<td>R-CH_2NH_2</td>
<td>NaBH_4</td>
<td>76-89%</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>R = H, 4-Me, 4-CO_2Me, 3-NO_2</td>
<td>CP_3CO_2H</td>
<td>THF</td>
<td>20°, 4 hr</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R-CN</td>
<td>R-CH_2CH_2NH_2</td>
<td>NaBH_4</td>
<td>70-71%</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>R = H, 4-NO_2, 4-Cl</td>
<td>CP_3CO_2H</td>
<td>THF</td>
<td>20°, 4 hr</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CN</td>
<td>CH_2NH_2</td>
<td>NaBH_4</td>
<td>70%</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>CH_3</td>
<td>CH_2NH_2</td>
<td>CP_3CO_2H</td>
<td>THF</td>
<td>20°, 4 hr</td>
</tr>
</tbody>
</table>

XI. REDUCTION OF AMIDES AND CARBAMATES

As is the case with nitriles (vide supra), amides are not reduced under conditions which produce NaBH(OCOR)_3. For example, we determined that 1-acetylindole and 1-acetylindoline were not reduced to 1-ethylindoline to any appreciable extent under conditions which convert indole to 1-ethylindoline in high yield (NaBH_4, excess HOAc).^11 For other examples of
amides (and similar carbonyls) that are not reduced under these conditions, see Table 3, entries 2, 3, 5; Table 4, entries 5, 7, 8, 14-16; Table 6, entry 25; Table 15, entries 1, 15.

However, Umino and coworkers have shown that the more reactive NaBH₄CCOR (R = CH₃, CF₃) are capable of reducing amides and carbamates to amines (Table 12). Tertiary amides require NaBH₄CCOCF₃ for reduction (entries 3, 4), whereas primary and secondary amides are reduced by NaBH₄OAc. Although carbamates can also be reduced under these conditions (entries 11, 12), the t-BOC protecting group survived intact in the reduction of an amide with NaBD₃CCOCF₃ (entry 7).

**TABLE 12. Reduction of Amides**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CONH₂</td>
<td>CH₂NH₂</td>
<td>NaBH₄₄ CH₃CO₂H</td>
<td>76% 88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dioxane Δ, 4 hr</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NHAc</td>
<td>NHEt</td>
<td>NaBH₄₄ CH₃CO₂H</td>
<td>88% 88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dioxane Δ, 1 hr</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ac</td>
<td>Ét</td>
<td>NaBH₄₄ CF₃CO₂H</td>
<td>64% 88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(28% with HOAc)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dioxane Δ, 5 hr</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>NaBH₄₄ CF₃CO₂H</td>
<td>83% 89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF Δ, 4 hr</td>
<td></td>
</tr>
</tbody>
</table>

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SODIUM BOROHYDRIDE IN CARBOXYLIC ACID MEDIA. A REVIEW

5. \[
\begin{align*}
\text{SCH}_3 & \quad \text{CONHCH}_2\text{CH}_2\text{OH} & \text{NaBH}_4 & 80\% 90 \\
\text{CH}_3 & & \text{HOAc} & \\
& & \text{dioxane} & \\
& & \Delta, 2 \text{ hr} & \\
\end{align*}
\]

6. \[
\begin{align*}
\text{C}_2\text{H}_5 & \quad \text{NHCO} & \quad \text{Me}_2\text{C} & \quad \text{NH} & \quad \text{Me}_2\text{C} \\
\text{O}_2\text{C} & & \text{NH}_2 & \quad \text{Me}_2\text{C} & \quad \text{NHCO}_2 \quad \text{D}_{25} \\
& & & & \text{NaBD}_3\text{O}_2\text{CCF}_3 & -- 92 \\
\end{align*}
\]

7. \[
\begin{align*}
\text{O}_2\text{CNH} & \quad \text{N} & \quad \text{NHCO}_2 \quad \text{D}_{25} \\
\end{align*}
\]

8. \[
\begin{align*}
\text{CF}_3\text{CO}_2\text{H} & \quad \text{NaBH}_4 & 58\% 59 \\
\text{THF} & & \\
\end{align*}
\]

9. \[
\begin{align*}
\text{CF}_3\text{CO}_2\text{H} & \quad \text{NaBH}_4 & 32\% 59 \\
\text{THF} & & \\
\end{align*}
\]

10. \[
\begin{align*}
\text{CF}_3\text{CO}_2\text{H} & \quad \text{NaBH}_4 & 76\% 13 \\
\text{tol, 6 hr} & & \\
\text{30-40°} & & \\
\end{align*}
\]

11. \[
\begin{align*}
\text{CH}_2\text{CF}_3 & \quad \text{NaBH}_4 & 66\% 88 \\
\text{HOAc} & & \\
\text{dioxane} & & \\
\Delta, 5 \text{ hr} & & \\
\end{align*}
\]

12. \[
\begin{align*}
\text{MeO} & \quad \text{NHCOCH}_2\text{Ph} & \quad \text{MeO} & \quad \text{NHCH}_3 & \quad \text{MeBH}_4 & 82\% 88 \\
\text{MeO} & \quad \text{NHCOCH}_2\text{Ph} & \quad \text{MeO} & \quad \text{NHCH}_3 & & \\
\text{HOAc} & & \text{dioxane} & & \Delta, 5 \text{ hr} & \\
\end{align*}
\]

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XII. HYDROBORATION OF ALKENES

The second reported use of NaBH₄/RCO₂H in synthesis—also described by Marshall and Johnson⁹³—was the hydroboration of alkenes. Although this method has not been widely used as such, several examples are known (Table 13). It is presumed that the hydroboring agent is NaBH₃OAc from the work of Hach⁹⁵ who optimized the reaction conditions. This would explain the apparent lack of hydroboration of alkenes under conditions that generate NaBH(OCOR)₃ (e.g., Table 6, entry 5; Table 10, entries 3, 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>1. NaBH₄</td>
<td>75%</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. H₂O₂,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OH⁻</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>1. NaBH₄</td>
<td>79%</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. H₂O₂,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OH⁻</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>1. NaBH₄</td>
<td>85%</td>
<td>95</td>
</tr>
<tr>
<td>(others)</td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10–20°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. H₂O₂,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OH⁻</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>1. NaBH₄</td>
<td>73%</td>
<td>96a</td>
</tr>
<tr>
<td>(others)</td>
<td></td>
<td></td>
<td>THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc, 20°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. H₂O₂,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OH⁻</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>1. LiBH₄</td>
<td>95%</td>
<td>96a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF, 20°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HOAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. H₂O₂,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OH⁻</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
XIII. REDUCTION OF ALKENES

A second reaction of alkenes with NaBH₄/RCO₂H that has been observed in one case is reduction (Eq. 21). Thus far, this alkene reduction is restricted to alkenes that can form a resonance-stabilized carbocation (e.g., doubly benzylic) in trifluoroacetic acid (TFA).

\[
\begin{align*}
\text{CH}_2 & \quad \text{NaBH}_4 \\
\text{C}_6\text{H}_5 & \quad \text{CF}_3\text{CO}_2\text{H} \\
\text{CH}_3 & \quad 93\%
\end{align*}
\]

The use of TFA in this regard is discussed further in the next two sections.

XIV. REDUCTION OF ALCOHOLS

Trifluoroacetic acid, which is an excellent solvent for solvolysis and other $S_{N1}$ reactions (ionizing power $Y$ value = 1.84), proves to be an ideal solvent with which to reduce diarylmethanols and triarylmethanols to the corresponding hydrocarbons with NaBH₄. This reduction method has proven to be exceedingly general and highly efficient (Table 14). Although yields are generally lower for monobenzylic alcohols (entries 20-22), in some cases it has been very successful (entries 17, 18). Reduction of benzyl alcohol, 1- and 2-octanol, and 1-methylcyclohexanol under these conditions is not observed. The reduction is very slow or fails in glacial HOAc, at least with triphenylmethanol.

In most of the cases that we have studied, the reaction is complete in seconds and can be monitored visually. Thus, the carbocation, which is usually highly colored, forms instantly as the alcohol is added to the suspension of NaBH₄.
in TFA, but then is rapidly quenched (color disappears) to give product. In one case (entry 19), the intermediate carbocation cyclizes faster than it undergoes reduction. In the case of several monobenzyllic alcohols (entries 20–22), other products, resulting from dehydration and dimerization (entries 20, 21) or alkylation of the product by the carbocation (entry 22), are observed.

**TABLE 14. Reduction of Alcohols**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>NaBH₄ CF₃CO₂H 15–20°</td>
<td>93%</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>NaBH₄ CF₃CO₂H 0° 5 min</td>
<td>97%</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>NaBH₄ CF₃CO₂H CH₂Cl₂ 15–20°</td>
<td>99%</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>NaBH₄ CF₃CO₂H 15–20°</td>
<td>94%</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>NaBH₄ CF₃CO₂H CH₂Cl₂</td>
<td>90%</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Substrate 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>NaBH₄ CF₃CO₂H CH₂Cl₂ 15–20°</td>
<td>86%</td>
<td>97</td>
</tr>
</tbody>
</table>

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7  
\[ \begin{align*}  
\text{NaBH}_4 & \quad 94\% \quad 97 \\
\text{CF}_3\text{CO}_2\text{H} & \\
\text{CH}_2\text{Cl}_2 & 15\% - 20\% 
\end{align*} \]

8  
\[ \begin{align*}  
\text{NaBH}_4 & \quad 77\% \quad 97 \\
\text{CF}_3\text{CO}_2\text{H} & \\
\text{CH}_2\text{Cl}_2 & 15\% - 20\% 
\end{align*} \]

9  
X = H, I, Br, NH\(_2\)  
Y = NMe\(_2\), OEt  
\[ \begin{align*}  
\text{NaBH}_4 & \quad 98-100\% \quad 97 \\
\text{CF}_3\text{CO}_2\text{H} & \\
\text{CH}_2\text{Cl}_2 & 5 \text{ min} 
\end{align*} \]

10  
\[ \begin{align*}  
\text{NaBH}_4 & \quad 78\% \quad 99 \\
\text{CF}_3\text{CO}_2\text{H} & \\
\text{CH}_2\text{Cl}_2 & -- \quad 100 
\end{align*} \]

11  
\[ \begin{align*}  
\text{NaBH}_4 & \quad 94\% \quad 101 \\
\text{CF}_3\text{CO}_2\text{H} & \\
\text{CH}_2\text{Cl}_2 & 0^\circ \text{C} \quad 2 \text{ hr} 
\end{align*} \]
GRIFFLE AND NUTAITIS

13

14

(1,1 isomer also)

15

16

17

18

\[ \text{NaBH}_4 \quad \text{CF}_3\text{CO}_2\text{H} \quad 89\% \quad 102 \] (from ketone)

\[ \text{NaBH}_4 \quad \text{CF}_3\text{CO}_2\text{H} \quad 88\% \quad 102 \] (from ketone)

\[ \text{NaBH}_4 \quad \text{CF}_3\text{CO}_2\text{H} \quad 95\% \quad 103 \]

\[ \text{NaBH}_4 \quad \text{CF}_3\text{CO}_2\text{H} \quad \text{CH}_2\text{Cl}_2 \quad 0\degree \text{C} \quad 2 \text{ hr} \quad 90 : 10 \] 60\% 103

\[ \text{NaBH}_4 \quad \text{CF}_3\text{CO}_2\text{H} \quad \text{CH}_2\text{Cl}_2 \]

\[ \text{NaBH}_4 \quad \text{CF}_3\text{CO}_2\text{H} \quad -- \quad 104 \]

\[ \text{NaBH}_4 \quad \text{CF}_3\text{CO}_2\text{H} \quad 75-82\% \quad 105 \] (from ketone)

R = Me, n-Pr, n-Hex
SODIUM BOROHYDRIDE IN CARBOXYLIC ACID MEDIA. A REVIEW

19
\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{OH} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]
\[
\text{NaBH}_4 \quad \begin{align*}
\text{CF}_3\text{CO}_2\text{H} \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]
\[
15-20^\circ
\]
\[93\%~97\]

20
\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{OH} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]
\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]
\[
\text{NaBH}_4 \quad \begin{align*}
\text{CF}_3\text{CO}_2\text{H} \\
0^\circ
\end{align*}
\]
\[
15-20^\circ
\]
\[70\%~97\]

21
\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{OH} & \quad \text{Ph}
\end{align*}
\]
\[
\text{NaBH}_4 \quad \begin{align*}
\text{CF}_3\text{CO}_2\text{H} \\
15-20^\circ
\end{align*}
\]
\[45\%~97\]

22
\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{OH} & \quad \text{Ph}
\end{align*}
\]
\[
\text{NaBH}_4 \quad \begin{align*}
\text{CF}_3\text{CO}_2\text{H} \\
15-20^\circ
\end{align*}
\]
\[9\%~97\]

23
\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]
\[
\text{NaBH}_4 \quad \begin{align*}
\text{CF}_3\text{CO}_2\text{H} \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]
\[
15-20^\circ
\]
\[97\%~51\]

XV. REDUCTION OF KETONES TO HYDROCARBONS

The companion reaction to the reduction of diarylmethanols to diarylmethanes with NaBH$_4$/TFA (Section XIV) is the reduction of diarylketones to diarylmethanes under the same conditions (Table 15). This reaction is very efficient and general, and in some cases works well for monoaryl ketones (entries 14, 15, 22). However, Michler's ketone (4,4'-bis-[dimethylamino]benzophenone) and decafluorobenzophenone fail to
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react with NaBH₄/CF₃CO₂H, and the reduction of 4-nitrobenzo-phenone (entry 2) is very slow. Likewise, the sterically hindered diarylketones mesityl phenyl ketone, dimesityl ketone, and mesityl α-naphthyl ketone give little or no reduction product.¹⁰⁶ Depending on the mode of addition, anthrone may be reduced either to dihydroanthracene (entry 7) or to anthracene (entry 8). In unpublished work, we have found that quinones are reduced either to a fully reduced compound (entry 11) or to the corresponding aromatic hydrocarbon (entry 12). 1,4-Naphthoquinone and 9,10-anthraquinone are also reduced to their respective aromatic hydrocarbons in variable yields.⁵¹ Smith and coworkers¹¹¹-¹¹² have developed a facile two-carbon homologation sequence using the NaBH₃CN/HOAc reduction of acylated Meldrum's acid and related derivatives (entries 16-21).

TABLE 15. Reduction of Ketones to Hydrocarbons

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Ketone Structure" /></td>
<td><img src="image2" alt="Hydrocarbon Structure" /></td>
<td>NaBH₄/CF₃CO₂H/CH₂Cl₂, 15-20°C</td>
<td>73-94%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Ketone Structure" /></td>
<td><img src="image4" alt="Hydrocarbon Structure" /></td>
<td>NaRh₄/CF₃CO₂H/CH₂Cl₂, 15-20°C</td>
<td>43%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Ketone Structure" /></td>
<td><img src="image6" alt="Hydrocarbon Structure" /></td>
<td>NaRh₄/CF₃CO₂H/CH₂Cl₂, 15-20°C</td>
<td>91%</td>
</tr>
</tbody>
</table>

362
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Reaction Conditions</th>
<th>Product Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Structure 4" /></td>
<td>NaBH₄, CF₃CO₂H, CH₂Cl₂, 15-20°C</td>
<td>91% 106</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2.png" alt="Structure 5" /></td>
<td>NaBH₄, CF₃CO₂H</td>
<td>-- 107</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3.png" alt="Structure 6" /></td>
<td>NaBH₄, CF₃CO₂H, CH₂Cl₂, 15-20°C</td>
<td>85% 106</td>
</tr>
<tr>
<td>7</td>
<td><img src="image4.png" alt="Structure 7" /></td>
<td>NaBH₄, CF₃CO₂H, (added last) CH₂Cl₂, 15-20°C</td>
<td>91% 106</td>
</tr>
<tr>
<td>8</td>
<td><img src="image5.png" alt="Structure 8" /></td>
<td>NaBH₄, CF₃CO₂H, CH₂Cl₂, 15-20°C</td>
<td>78% 106</td>
</tr>
<tr>
<td>9</td>
<td><img src="image6.png" alt="Structure 9" /></td>
<td>NaBH₄, CF₃CO₂H, CH₂Cl₂, 15-20°C</td>
<td>88% 106</td>
</tr>
<tr>
<td>10</td>
<td><img src="image7.png" alt="Structure 10" /></td>
<td>NaBH₄, CF₃CO₂H</td>
<td>85% 108</td>
</tr>
<tr>
<td>11</td>
<td><img src="image8.png" alt="Structure 11" /></td>
<td>NaBH₄, CF₃CO₂H, 15-25°C</td>
<td>57% 51</td>
</tr>
<tr>
<td>12</td>
<td><img src="image9.png" alt="Structure 12" /></td>
<td>NaBH₄, CF₃CO₂H, 10-20°C</td>
<td>23% 51</td>
</tr>
</tbody>
</table>
GRIBBLE AND NUTAITIS

13

\[
\text{R} = \text{Me, n-Pr, n-Hex}
\]

14

\[
\text{R} = \text{Me, n-Pr, n-Hex}
\]

15

\[
\text{CONMe}_2
\]

16

\[
\text{R} = \text{Et, i-Pr, CH}_2\text{Ph}
\]

17

\[
\text{R} = \text{n-Pr, i-Bu, n-Pen, n-C}_15\text{H}_31
\]

\[
\text{R'} = \text{H, Me}
\]

18

\[
\text{R} = \text{Et, n-Pr, n-Bu, n-C}_15\text{H}_31
\]

19

\[
\text{NaBH}_4\ \text{CF}_3\text{CO}_2\text{H}
\]

\[
15-20^\circ
\]

\[
86\% \ 51
\]

\[
\text{NaBH}_4\ \text{CF}_3\text{CO}_2\text{H}
\]

\[
75-88\% \ 105
\]

\[
\text{NaBH}_4\ \text{CF}_3\text{CO}_2\text{H}
\]

\[
0^\circ \ \text{25^\circ}
\]

\[
76\% \ 109
\]

\[
\text{NaBH}_4\ \text{CN}
\]

\[
\text{HOAc}
\]

\[
50-85\% \ 111
\]

\[
\text{NaBH}_4\ \text{CN}
\]

\[
\text{HOAc}
\]

\[
75-96\% \ 111
\]

\[
\text{NaBH}_4\ \text{CN}
\]

\[
\text{HOAc}
\]

\[
78-86\% \ 111
\]

\[
\text{NaBH}_4\ \text{CN}
\]

\[
\text{HOAc}
\]

\[
70\% \ 111
\]

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20

\[
\begin{align*}
\text{NaBH}_3\text{CN} & \quad 74-84\% 112 \\
\text{HOAc} & \\
\text{THF} & \\
65^\circ & \\
2 \text{ hr} & \\
\end{align*}
\]

\[
\begin{align*}
\text{C}=\text{O} & \quad \text{(CH}_2\text{)}_{n+2} \\
\text{C}=\text{O} & \\
\text{NaBH}_3\text{CN} & \quad 75\% 113 \\
\text{HOAc} & \\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{Ph, Me} &
\end{align*}
\]

21

\[
\begin{align*}
\text{NaBH}_3\text{CN} & \quad 75\% 113 \\
\text{HOAc} & \\
\end{align*}
\]

22

\[
\begin{align*}
\text{NaBH}_4 & \quad 99\% 51 \\
\text{CF}_3\text{CO}_2\text{H} & \\
\text{CH}_2\text{Cl}_2 & \\
15-20^\circ & \\
\end{align*}
\]

XVI. ACYLATION OF ALCOHOLS AND AMINES

In what could be considered as a side-reaction in the chemistry of NaBH\textsubscript{4}/RCO\textsubscript{2}H, the acylation of suitable functional groups (e.g., alcohols, phenols, amines) is frequently encountered. Indeed, the isolation of methyl formate by Wartik and Pearson\textsuperscript{6} (Section I) is an example of the acylation (formylation) of methanol by a formyloxyboron species. Apparently independently, two groups have developed this into a useful alcohol and phenol acylation method (Table 16). It is presumed that under the reaction conditions (excess RCO\textsubscript{2}H, reflux, 3 hr)\textsuperscript{12} the acylating agent is NaB(OCOR)\textsubscript{4} or even B(OCOR)\textsubscript{3} (plus NaO\textsubscript{2}CR).
# TABLE 16. Acylation of Alcohols, Phenols and Thiophenols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="OH" /></td>
<td><img src="image" alt="OAc" /></td>
<td>NaBH₄, HOAc, Δ, 3 hr</td>
<td>95%</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="OH" /></td>
<td><img src="image" alt="OAc" /></td>
<td>NaBH₄, HOAc, Δ, 3 hr</td>
<td>50%</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="OH" /></td>
<td><img src="image" alt="COEt" /></td>
<td>NaBH₄, EtCO₂H, 85-90°, 3 hr</td>
<td>80%</td>
<td>114</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="OH" /></td>
<td><img src="image" alt="OAc" /></td>
<td>NaBH₄, HOAc, 85-90°, 3 hr</td>
<td>90-95%</td>
<td>114</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="OH" /></td>
<td><img src="image" alt="OAc" /></td>
<td>NaBH₄, HOAc, Δ, 12 hr</td>
<td>80-98%</td>
<td>114</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="SH" /></td>
<td><img src="image" alt="SAc" /></td>
<td>NaBH₄, HOAc, Δ, 12 hr</td>
<td>75-95%</td>
<td>114</td>
</tr>
</tbody>
</table>

R = H, Me, Cl

Amines can be similarly acylated to form amides (Table 17).
TABLE 17. Acylation of Amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{NH}_2)</td>
<td>(\text{NHCEt})</td>
<td>(\text{NaBH}_4) Et(\text{CO}_2\text{H}) (\Delta, 3\text{ hr})</td>
<td>95%</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>(\text{H-N-N-N})</td>
<td>(\text{N.Ac})</td>
<td>(\text{NaBH}_4) HOAc (\Delta, 3\text{ hr})</td>
<td>40%</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>(\text{N.H})</td>
<td>(\text{N.Et})</td>
<td>(\text{NaBH}_4) Et(\text{CO}_2\text{H}) (\Delta, 3\text{ hr})</td>
<td>60%</td>
<td>12</td>
</tr>
</tbody>
</table>

XVII. REDUCTION OF ALDEHYDES AND KETONES TO ALCOHOLS

Early in our exploration of the chemistry of \(\text{NaBH}_4/\text{RCO}_2\text{H}\), we observed that aldehydes and, especially, ketones are reduced more slowly to alcohols by \(\text{NaBH}_4\) in glacial acetic acid than in alcoholic solution. For example, although benzaldehyde is completely reduced to benzyl alcohol, acetophenone and benzophenone are incompletely reduced to their alcohols with a large excess of \(\text{NaBH}_4\) in glacial acetic acid (Eqs. 22-24). Even after these long reaction periods active borohydride reagent is present at the end of the reaction. In contrast, both of these ketones are rapidly and completely reduced to their respective alcohols with \(\text{NaBH}_4\) in ethanol.
These observations paved the way for the chemoselective reduction of aldehydes, in the presence of ketones, using NaBH(OAc)$_3$ in benzene$^{115}$ or, even better, $n$-Bu$_4$NBH(OAc)$_3$ in benzene.$^{116}$ In both cases excess hydride reagent can be used. Examples of this chemoselective reduction of aldehydes to primary alcohols, in the presence of ketones, are tabulated in Table 18.

**TABLE 18. Reduction of a 1:1 Mixture of Aldehyde and Ketone With $n$Bu$_4$NBH(OAc)$_3$ in Benzene (24 hr, reflux)$^{116}$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Ketone</th>
<th>Yield of Primary Alcohol</th>
<th>Yield of Recovered Ketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Aldehyde Structure]</td>
<td>![Ketone Structure]</td>
<td>95%</td>
<td>96%</td>
</tr>
</tbody>
</table>
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<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>95%</td>
<td>99%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>90%</td>
<td>94%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>80%</td>
<td>92%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>87%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Moreover, as shown in Table 19, several ketoaldehydes have been reduced selectively to ketoalcohols or, in those cases where the hydroxyl group can complex with the borohydride species, to 1,3-diols (entry 4). Indeed, this method has been used by Saksena\textsuperscript{119} to reduce \( \beta \)-hydroxyketones to 1,3-diols with complete stereoselectivity (OH-assisted hydride delivery) (entries 7, 8). A related reduction has been described by Fuchs,\textsuperscript{120} involving an \( \alpha \)-hydroxyketone (entry 9).
### TABLE 19. Reduction of Ketocarboxylic Acid and Related Systems

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>88%</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>72%</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>77%</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>80%</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td>60%</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>--</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td>96%</td>
<td>119</td>
<td></td>
</tr>
</tbody>
</table>

R = Me, CH₂Ph, allyl

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\[
\begin{align*}
\text{NaBH}(OAc)_3 & \quad 90\% \ 119 \\
\text{HOAc} & \\
\text{THF} & \\
(\text{or CH}_2\text{Cl}_2) & \\
5 \text{ min} & \\
\text{NaBH}_3\text{CN} & \quad 92-96\% \ 120 \\
\text{CF}_3\text{CO}_2\text{H} & \\
3 \text{ hr} & \\
0-5^\circ & 
\end{align*}
\]

(others)

Several groups have examined the stereochemistry of cyclic ketone reduction using NaBH\(_4\)/RCO\(_2\)H (Table 20). Although the reduction of cyclohexanones is only moderately stereoselective with NaBH\(_4\)/HOAc, generally favoring the equatorial alcohol (entries 2, 3, 6), the stereoselectivity can be greatly enhanced by using acyloxyborohydride reagents derived from mandelic acid (entries 1, 5) or tartaric acid (entries 4, 7).

TABLE 20. Reduction of Cyclic Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield Ref.</th>
</tr>
</thead>
</table>
| 1     | \begin{align*}
\text{NaBH}_4 \\
\text{PhCH}^{-}\text{OH} \\
\text{CO}_2\text{H} \\
\text{i-PrOH}, \Delta \\
2 \text{ hr}
\end{align*} | \begin{align*}
8 & : 92 \\
(\text{others}) & \\
\end{align*} | -- 121 |
| 2     | \begin{align*}
\text{NaBH}_4 \\
\text{HOAc}
\end{align*} | \begin{align*}
26 & : 74
\end{align*} | 90\% 19 |
| 3     | \begin{align*}
\text{NaBH}_3\text{CN} \\
\text{HOAc}^-
\end{align*} | \begin{align*}
23 & : 77
\end{align*} | 95\% 19 |
Several groups have examined the asymmetric reduction of ketones with optically active acyloxyborohydrides (Table 21), in some cases achieving good enantioselectivity. For each study, only the best of several systems examined is shown in Table 21.

**TABLE 21. Asymmetric Reduction of Ketones**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td><strong>NaBH₄</strong> i-PrCO₂H THF, 25°C</td>
<td>63% ee (R)</td>
<td>56% 123</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td><strong>NaBH₄</strong> PhCHCO₂H Et₂, THF 2 hr, rt sugar</td>
<td>51% ee (R)</td>
<td>68% 124</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td><strong>NaBH₄</strong> THF, rt 10 days proline</td>
<td>50% ee (S)</td>
<td>92% 125</td>
</tr>
</tbody>
</table>
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Finally, the interesting double reduction of the ketone and enol acetate functionalities in a nucleoside has been reported, accompanied by an acetyl transposition (Eq. 25).\textsuperscript{126}

\[
\begin{align*}
\text{NaBH}_4 & \quad \text{dioxane} \\
\Delta, & \quad 4 \text{ hF} \\
\text{Ph-CH}_2 & \quad \text{OH} \\
\text{CO}_2 & \quad \text{H}
\end{align*}
\]

11.5\% ee \ (R)

(25)

XVIII. REDUCTIVE CLEAVAGE OF ACETALS, KETALS, AND ETHERS

As might be expected, the use of trifluoroacetic acid in combination with NaBH\textsubscript{4} can effect the reductive cleavage of acetics, ketals, and ethers. A few examples have been reported (Table 22). The yields are higher for those systems giving rise to phenyl-stabilized oxonium ions (entries 1-3, 5 vs. entry 4). Recently, the deoxygenation of an ozonide was reported (entry 6).\textsuperscript{133}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO</td>
<td>Ar-HO</td>
<td>NaBH\textsubscript{4}CN, CP\textsubscript{3}CO\textsubscript{2}H, DMF</td>
<td>85%</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>(others)</td>
<td>Ph-Me</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 22. Reductive Cleavage of Acetals, Ketal, and Ethers

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NaBH₄  11-83%  128
CF₃CO₂H
THF
20°, 5 hr

NaBH₄  78%  128
CF₃CO₂H
THF
20°, 5 hr

NaBH₄  33-40%  128
CF₃CO₂H
THF
Δ, 24 hr

NaBH₄  57-97%  129
CF₃CO₂H

NaBH₄  40%  133
CF₃CO₂H
20°, 30 min

(others)

XIX. FRIEDEL-CRAFTS ALKYLATION OF ARENES

During our studies¹¹,⁵⁹ of the reaction of indole (or indoline) with NaBH₄/CF₃CO₂H, we observed the formation of an interesting bis-indole product (Eq. 26).

(26)
More recently, we have found\textsuperscript{130} that this "Baeyer condensation"\textsuperscript{131} is general for activated arenes and generally furnishes the \textit{p,p}'-isomer in fair to good yield (Table 23). The reaction fails with benzene, toluene, and \textit{p}-xylene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate1" /></td>
<td><img src="image2" alt="Product1" /></td>
<td>\text{NaBH}_4/\text{CF}_3\text{CO}_2\text{H} (60^\circ\text{C})</td>
<td>34%</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate2" /></td>
<td><img src="image4" alt="Product2" /></td>
<td>\text{NaBH}_4/\text{CF}_3\text{CO}_2\text{H} (\Delta)</td>
<td>52%</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate3" /></td>
<td><img src="image6" alt="Product3" /></td>
<td>\text{NaBH}_4/\text{CF}_3\text{CO}_2\text{H} (\Delta)</td>
<td>22%</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate4" /></td>
<td><img src="image8" alt="Product4" /></td>
<td>\text{NaBH}_4/\text{CF}_3\text{CO}_2\text{H} (\Delta)</td>
<td>46%</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate5" /></td>
<td><img src="image10" alt="Product5" /></td>
<td>\text{NaBH}_4/\text{CF}_3\text{CO}_2\text{H} (\Delta)</td>
<td>47%</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Substrate6" /></td>
<td><img src="image12" alt="Product6" /></td>
<td>\text{NaBH}_4/\text{CF}_3\text{CO}_2\text{H} (\Delta, 3\text{ hr})</td>
<td>53%</td>
<td>130</td>
</tr>
</tbody>
</table>
XX. SUMMARY

In this review we have tried to illustrate the versatility of the relatively new acyloxyborohydride class of reducing agents. We have shown how, by changing carboxylic acid, solvent, stoichiometry, temperature, time, and hydride reagent itself, one can achieve remarkable chemoselectivity in an array of different types of reactions.

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