<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Reduction of N,N-dimethylcarboxamides to aldehydes by sodium hydride-iodide composite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author(s)</strong></td>
<td>Chan, Guo Hao; Ong, Derek Yiren; Yen, Zhihao; Chiba, Shunsuke</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>2018</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10220/48234">http://hdl.handle.net/10220/48234</a></td>
</tr>
<tr>
<td><strong>Rights</strong></td>
<td>© 2018 Wiley-VHCA AG, Zurich, Switzerland. All rights reserved. This paper was published in Helvetica Chimica Acta and is made available with permission of Wiley-VHCA AG, Zurich, Switzerland.</td>
</tr>
</tbody>
</table>
Reduction of N,N-Dimethylcarboxamides to Aldehydes by Sodium Hydride-Iodide Composite

Guo Hao Chan,a Derek Yiren Ong,a Zhihao Yen,a and Shunsuke Chiba*,a

a Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371 (Singapore) e-mail: shunsuke@ntu.edu.sg

A new and concise protocol for selective reduction of N,N-dimethylamides into aldehydes was established using sodium hydride (NaH) in the presence of sodium iodide (NaI) under mild reaction conditions. The present protocol with the NaH-NaI composite allows for reduction of not only aromatic and heteroaromatic but also aliphatic N,N-dimethylamides with wide substituent compatibility. Retention of α-chirality in the reduction of α-enantiomeriched amides was accomplished. Use of sodium deuteride (NaD) offers a new step-economical alternative to prepare deuteriated aldehydes with high deuterium incorporation rate. The NaH-NaI composite exhibits unique chemoselectivity for reduction of N,N-dimethylamides over ketones.

Keywords: Amides • Aldehydes • Reduction • Sodium hydride • Iodide

Introduction

Hydride reduction of carbonyl compounds is one of the most fundamental and important processes in organic synthesis[1-2]. Among various carbonyl compounds, bench-stable amides are used as a versatile precursor to be reduced into amines and alcohols as well as aldehydes (Scheme 1)[3-6]. Especially, to perform the efficient and selective reduction of amides into aldehydes, specific setups in the amide substituents, the reductants, and/or the reaction conditions are required to prevent fragmentation of transient tetrahedral metalated aminal intermediates, that results in over-reduction to amines or alcohols.

Scheme 1. Reduction of amides.

For this purpose, N-methoxy-N-methylamides (the Weinreb amides), that form stabilized tetrahedral five-membered-chelate intermediates[7-9], have typically been utilized with reactive hydride donors such as lithium aluminum hydride, diisobutylaluminum hydride, and Red-Al under cryogenic reaction conditions (commonly at < 0 °C) (Scheme 2A)[10]. There has also been reported use of tertiary amides having special substituents which reduce the electron-donating nature of the amide nitrogen onto the carbonyl group, including N-acylsultam[11], N-acylsaccharin[12], N-acyl carbazoles[13] and N-acylaziridines (Scheme 2B)[14-15].

A. Weinreb amides

B. Other specialized amides

Scheme 2. Special setups onto amides for reduction to aldehydes

On the other hand, the reduction of simple N,N-dialkylamides to aldehydes needs use of modified hydride reagents such as LiAIH₄(OT)₂κ₁ (n = 1 or 2)[16-17], disiamylborane[18], and lithium disobutylpiperidinohydroaluminate[19]. It should be noted that the Schwartz’s reagent [C₆Zr(H)Cl]₂ is capable of reducing a variety of amides (primary, secondary, and tertiary) to the corresponding aldehydes under very mild reaction conditions with wide functional group compatibility (Scheme 3A)[20-22]. There have been reported several methods for reduction of amides to aldehydes using hydrosilanes with the aid of transition metals. Buchwald developed reduction of aliphatic amides into aldehydes by combined use of Ph₂SiH₂ and Ti(O₂Pr)₄, that proceeds via formation of an enamine intermediate (Scheme 3B)[23]. Therefore, racemization is observed in the reduction of α-enantiomeriched amides. Adolfsson disclosed versatile reduction of piperidine amides into aldehydes with 1,1,3,3-tetramethyldisiloxane catalyzed by Mo(CO)₆ (Scheme 3C)[24]. Temperature control is the key to enable selective formation of
aldehydes over that of amines (−5 to 60 °C), in which unique chemoselectivity for the reduction of amides over other susceptible \( \pi \)-polar functional groups such as keto, formyl, and imine moieties was observed. On the other hand, transition-metal free reduction of secondary amides into aldehydes was reported by Charette (Scheme 3D)[25]. The process requires prior activation of amides with \( \text{Ti}_2\text{O} \) followed by reduction with \( \text{Et}_3\text{SiH} \).

A. with Schwartz’s reagent

\[
\begin{align*}
\text{R}^+ & \quad \text{Cp}_2\text{ZnHCl} \quad \text{THF, rt} \quad \text{R} - \text{H} \\
1^*, 2^*, 3^*-\text{amides} & \quad \text{R} = \text{aryl, alkyl}
\end{align*}
\]

B. with hydrodesilanes and Ti(OiPr)_4

\[
\begin{align*}
\text{R} - \text{O} & \quad \text{Ti(OiPr)}_4 \quad \text{Ph}_2\text{SiH}_2 \quad \text{neat, rt} \quad \text{via amine intermediates} \quad \text{R} - \text{N}^* \quad \text{R}^+ \\
2^*, 3^*-\text{amides} & \quad \text{R} = \text{aryl, alkyl}
\end{align*}
\]

C. with hydrodesilanes and Mo catalyst

\[
\begin{align*}
\text{R} - \text{O} & \quad \text{Mo(CO)}_3 \quad \text{SiO} \quad \text{Si} \quad \text{H} \quad \text{H} \quad \text{R} - \text{H} \\
\text{piperidine amides} & \quad \text{R} = \text{aryl, alkyl}
\end{align*}
\]

D. with hydrodesilanes through electrophilic activation of 2^*-amides

\[
\begin{align*}
\text{R} - \text{O} & \quad \text{TiF}_4 \quad \text{2-F-pyridine} \quad \text{CH}_2\text{Cl}_2 \quad \sim 78 \text{ to } 0 ^\circ \text{C} \quad \text{R} - \text{N}^* \quad \text{R}^+ \\
\text{R} = \text{aryl, alkyl}
\end{align*}
\]

Scheme 3. Reduction of simple N,N-dialkylamides into aldehydes

Despite the recent progress, there is still ample room to develop methods for reducing simple amides into aldehydes, that can be conducted in operationally simple and cost-effective manners under milder reaction conditions. We recently disclosed that sodium hydride (NaH) could act as a hydride donor in the presence of NaI or LiI in THF, capable of performing a series of unprecedented hydride reduction such as hydrodecyanation of carbonitriles (Scheme 4A)[26-27], hydrodehalogenation of haloarenes (Scheme 4B)[28], and dearylation of arylphosphine oxides[29] (Scheme 4C)[30-31]. In this context, we envisioned that use of the sodium hydride-iodide composite for the reduction of amides results in unique outcomes.

This article describes a full account on hydride reduction of amides to aldehydes by the sodium hydride-iodide composite with broad evaluation in scope and limitations (Scheme 4D).

\[\text{Scheme 4. Reduction by the NaH-I composite}\]

A. Hydrodecyanation

\[
\begin{align*}
\text{CN} & \quad \text{OMe} \quad \text{NaH (2 equiv)} \quad \text{LiI (1 equiv)} \quad \text{THF, 85 °C} \quad \text{Ar} - \text{N}^* \quad \text{Na}^+ \\
\text{(Ar = 3-MeO-C}_6\text{H}_4\text{H}) & \quad 96%
\end{align*}
\]

B. Hydrodecylation

\[
\begin{align*}
\text{Br} & \quad \text{Ar} \quad \text{NaH (5 equiv)} \quad \text{LiI (2 equiv)} \quad \text{THF, 50 °C} \quad \text{H} - \text{N}^* \quad \text{H}^+ \quad \text{Na}^+ \quad \text{Li}^+ \\
\text{(NaI)} & \quad \text{(E^+ = C-electrophiles)}
\end{align*}
\]

C. Dearylation of arylphosphine oxides

\[
\begin{align*}
\text{Ph}_2\text{P} & \quad \text{Ph}_2\text{P} \quad \text{NaH (2 equiv)} \quad \text{LiI (1 equiv)} \quad \text{THF, 60 °C} \quad \text{E^+} \quad \text{0 °C, time} \quad \text{Ph}_2\text{P} \quad \text{Ph}_2\text{P} \\
\text{(E^+ = C-electrophiles)} & \quad \text{Ph}_2\text{P} \quad \text{Ph}_2\text{P}
\end{align*}
\]

D. Reduction of amides to aldehydes (this work)

\[
\begin{align*}
\text{R} - \text{NMe}_2 & \quad \text{NaH (3 equiv)} \quad \text{NaI (1 equiv)} \quad \text{THF, 40 °C} \quad \text{R} - \text{H} \quad \text{R} = \text{aryl, heteroaryl} \quad 1^*, 3^* - \text{alkyl}
\end{align*}
\]

Results and Discussion

Our preliminary investigation revealed that the reaction of \( N,N \)-dimethyl-2-naphthamide (1a) with NaH (3 equiv) and NaI (1 equiv) in THF at 85 °C (under sealed reaction conditions) completed within 1 h to give 2-naphthaldehyde (2a) in 90% yield as a sole product (Table 1, entry 1). Surprisingly, the transient tetrahedral hemiaminal intermediate could be kept stable even at high reaction temperature (85 °C), enabling selective formation of aldehyde 2a. This unprecedented discovery stimulated us further to optimize the reaction conditions to render the reduction process more selective and versatile. Slower reaction rate was observed when the iodide additive was changed to LiI (entry 2). We found that with the NaH-Nal system, lowering of the reaction temperature to 40 °C could also complete the process and the yield of 2a was improved to 93% (entry 3). Implementation of the reduction at 40 °C, despite longer reaction time required, is advantageous to make the process more selective (vide infra). Further lowering of the reaction temperature to 25 °C or the amount of NaI to 0.1 equivalent made the process incomplete even after 24 h (entries 4 and 5). It should be noted that use of NaH in the absence of iodide additives is not sufficient to drive the hydride reduction (entry 6).

\[\text{Scheme 4. Reduction by the NaH-I composite}\]

1 For our preliminary communications on reduction of simple amides onto aldehydes, see: ref. 26 and ref. 31.
Table 1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodide (equiv)</th>
<th>Temp / °C</th>
<th>time (h)</th>
<th>Yield of 2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaI (1)</td>
<td>85</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>LiI (1)</td>
<td>85</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>NaI (1)</td>
<td>40</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>NaI (1)</td>
<td>25</td>
<td>24</td>
<td>(63)</td>
</tr>
<tr>
<td>5</td>
<td>NaI (0.1)</td>
<td>40</td>
<td>24</td>
<td>(23)</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>40</td>
<td>10</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] The reactions were conducted using 0.5 mmol of amide 1a in THF (0.2 M). [b] Isolated yields. [c] 1H NMR yield based on the internal standard. 1a was recovered in 36% yield. [d] 1H NMR yield based on the internal standard. 1a was recovered in 74% yield. [e] 1a was recovered in >95% yield based on the internal standard.

Having optimized the reaction conditions, we next investigated the substituent effect of the amide nitrogen (Scheme 5). We found that as the steric demand increases, the reaction becomes more sluggish. The reduction of diisopropylamide 1bc was not completed even after 24 h, providing only 7% yield of aldehyde 2b with 70% recovery of 1bc. Piperidine and morpholine amides 1bd and 1be showed similar reactivity as that of diethylamide 1bb.

Scheme 5. Investigation of the substituent effect on the amide nitrogen. [a] The reactions were conducted using 0.5 mmol of amides 1 with 3 equiv of NaH and 1 equiv of NaI in THF (0.2 M) at 40 °C and isolated yields of aldehydes 2 were noted above. [b] 1H NMR yield based on the internal standard. [c] 1l was recovered in 81% yield based on the internal standard. [d] The reaction was conducted using N,N,N',N'-tetramethylterephthalamide (1t) with 5 equiv of NaH and 2 equiv of NaI at 85 °C.

Reduction of various aromatic N,N-dimethylamides was next examined (Scheme 6). As electron-donating substituents, methoxy, methoxymethoxy (MOMO-), benzoxyl, and methylenedioxy as well as dimethylamino moieties could be tolerated, and the corresponding aldehydes were obtained in 78-94% yields (for 2b-2h). Sterically hindered benzamides having ortho-methyl (for 2i) and ortho-benzyl (for 2j) groups as well as 1-naphthamide 1k could be reduced smoothly, while reduction of 2,6-dimethylbenzamide 1l became sluggish. Synthesis of ferrocenecarboxaldehyde (2m) was achieved in 93% yield. It should be worthy of note that the present reaction conditions allowed for chemoselective reduction of amides into benzaldehydes keeping C-halogen bonds intact (for 2o-2r).

Reduction of electron-deficient amides 1s and 1t also worked well, while that of α,β-unsaturated amide 1u performed in moderate efficiency.

Scheme 6. Reduction of aromatic amides. [a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of amides 1 with 3 equiv of NaH and 1 equiv of NaI in THF (0.2 M) at 40 °C and isolated yields of aldehydes 2 were noted above. [b] 1H NMR yield with the aid of internal standard. [c] 1l was recovered in 81% yield based on the internal standard. [d] The reaction was conducted using N,N,N',N'-tetramethylterephthalamide (1t) with 5 equiv of NaH and 2 equiv of NaI at 85 °C.

We then shifted our attention to the reduction of heteroaromatic amides (Scheme 7). Various electron-rich 5-membered heteroaromatic substrates were first screened (Scheme 7A). Reduction of N-methyl-2-indolocarboxamide 3a and N-benzyl-2-pyrolecarboxamide 3b gave the corresponding aldehydes in excellent yields. N-Unprotected 2-pyrolecarboxamide 3c could be reduced in good yield, while use of 5 equivalents of NaH was required to complete the process. Other electron-rich heteroaromatic amides based on furan, thiophene, and benzothiophene could be
converted into the corresponding aldehydes in good to moderate yields (for 4d-4f). On the other hand, electron-deficient 6-membered-ring aromatic heterocycles are susceptible to the conventional hydride reductants. In this regard, use of the NaH-Nal composite is advantageous as quinoline and pyridine scaffolds were tolerated during the amide reduction. Various quinoline and pyridine carboxamides were reduced to the corresponding aldehydes in good to moderate yields. Nevertheless, this protocol is capable of reducing 7-chloro-2-phenylquinoline-4-carboxamide (3i) to 7-chloro-2-phenylquinoline-4-carboxaldehyde (4i), which is a key intermediate for supplying a quinolone-based anti-cancer agent[32].

We next turned our attention to the reduction of aliphatic amides (Scheme 8). Amides having an α-quaternary carbon are suitable substrates for the reduction (Scheme 8A), including the ones derived from drug molecule, gemfibrozil (for 6d) and natural product, abietic acid (for 6e). We also found that the reduction of α-tertiary amides having one enolizable proton gave the corresponding aldehydes in good yields, emphasizing the mild reaction conditions and functional group tolerance of the NaH-Nal system (Scheme 8B). The method is compatible with aldehydes based on aliphatic heterocycles such as tetrahydropyran 6i, piperidine 6j which is used for production of donepezil hydrochloride, an anti-Alzheimer drug[33], and pyrrolidine 6k. We also note that our reaction conditions were optimal for the reduction of α-secondary amide 5l.

It is particularly worthy to note that the current protocol is amenable to reduce α-enantiociched amides 5f and 5k in good yields and selectivity to afford the corresponding aldehydes in high ee (6k was further converted into alcohol 7k for the purpose to measure the ee by the Mosher method) (Scheme 9).
Scheme 9. Reduction of α-enantioriched amides. [a] The reactions were quenched by pouring the reaction mixture into pH7 phosphate buffer solution to prevent undesired epimerization (see the Supporting Information for details).

The reduction of aromatic amides 1a and 1b by NaD resulted in formation of the corresponding deuterated aromatic aldehydes 2a-[D] and 2b-[D] with high deuterium incorporation rate of 93% and 95%, respectively (Scheme 10). Similarly, the reduction of aliphatic amide 5a afforded 90% deuterium incorporation in 6a-[D]. These results unambiguously support that sodium hydride is acting as a hydride donor. Moreover, this protocol provides a direct and concise method to supply deuterated aldehydes with high deuterium incorporation rate, given the fact that existing methods involve use of expensive reagents and/or require multistep routes for their preparation (Scheme 10).

Scheme 10. Deuterium labeling experiments.

Conclusions

We have developed a new and concise protocol for selective reduction of N,N-dimethyl amides into aldehydes using the NaH-Nal composite under mild reaction conditions. The protocol is capable of reducing variety of amides ranging from aromatic and heteroaromatic amides to α-enantioriched aliphatic amides with retention of enantiomeric excess. Use of sodium deuteride (NaD) offers a new step-economical alternative to prepare deuterated aldehydes with high deuterium incorporation rate. The method exhibits unique chemoselectivity for reduction of amides over other carbonyl functions such as ketones. Further investigation of the reactivity of NaH-iodide composites to develop other types of hydride reduction processes is ongoing in our laboratory.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

Acknowledgements

This work was financially supported by Nanyang Technological University (NTU), Singapore Economic Development Board (EDB), Pfizer Asia Pacific Pte. Ltd., and the Singapore Ministry of Education (Academic Research Fund Tier 1: RG10/17). GHC thanks to EDB-Industrial Post-graduate Program (IPP) for the scholarship support. We thank Prof. Han Sen Soo and Mr. Zhonghan Hong (Division of Chemistry and Biological Chemistry, NTU) for the assistance in powder XRD experiments.
Author Contribution Statement

G.H.C., D.Y.O., and S.C. designed the studies. G.H.C., D.Y.O., and Z.Y. performed the experiments. G.H.C. and S.C. wrote the manuscript.

References


Entry for the Table of Contents

\[ \begin{align*}
\text{O} \quad & \quad \text{R} \quad \text{NMe}_2 \quad \xrightarrow{\text{NaH (3 equiv)}} \quad \text{O} \quad \text{R} \quad \text{H} \\
& \quad \text{THF, 40 °C} \quad \xrightarrow{\text{Nal (1 equiv)}} \quad \text{R = aryl, heteroaryl} \\
& \quad \text{1°-3° alkyl}
\end{align*} \]

- concise synthetic protocol
- retention of α-chirality
- concise and efficient deuterium incorporation using NaD
- chemoselective reduction of amides over ketones