HIGHLY REGIOSELECTIVE 1,4-ADDITION OF 2-LITHIO-2-(2,6-DIMETHYLPIPERIDINO)ACETONITRILE TO α,β-UNSATURATED KETONES

Takeshi Wakamatsu*, Satoshi Hobara, and Yoshio Ban
Faculty of Pharmaceutical Sciences, Hokkaido University,
Sapporo 060, Japan

Abstract — 2-Lithio-2-(2,6-dimethylpiperidino)acetonitrile, a formyl anion equivalent, readily reacts with α,β-unsaturated cyclic ketones to result in a successful conjugate 1,4-addition.

The Michael addition of formyl carbanion equivalents to α,β-unsaturated ketones is a very important reaction which constitutes formation of synthetically useful 1,4-dicarbonyl compounds. Although nitromethane and hydrogen cyanide are most commonly used reagents for formyl carbanion equivalents, conversion of the introduced nitromethyl or cyano group to the formyl group is not an easy process. Thus, there have been continuing interests in investigations on the conjugate 1,4-addition of a formyl anion or an equivalent to α,β-unsaturated ketones. For practical purposes, the latent formyl groups should be easily unmasked after the conjugate addition is effected.

To our knowledge, cyclic 2-enones have not been used for the Michael addition with α-aminoacetonitriles which are widely utilized as acyl carbanion equivalents.

We describe herein the successful utilization of the lithio α-aminoacetonitrile (1) in 1,4-addition to α,β-unsaturated cyclic ketones followed by unmasking to the formyl group and the effects of solvent and temperature on the addition.
2-(2,6-Dimethylpiperidino)acetonitrile\(^\text{10}\) which could be expected to increase the steric hindrance around the carbanion center was selected as a substrate with the reason for preventing the self-condensation reaction of a-aminoacetonitrile during anion formation. It has been found that the lithio derivative (1) derived from 2-(2,6-dimethylpiperidino)acetonitrile undergoes conjugate addition to 2-cyclopentenone (2) giving 1,4-adduct (3) as a sole product. A typical procedure is described in the following. 2-(2,6-Dimethylpiperidino)acetonitrile (6.5mM) in tetrahydrofuran (THF) was added at -78°C to lithium diisopropylamide (6.5mM) in THF (100.2mL) under argon. Thereafter were added hexamethylphosphoramide (HMPA) (16mM) and then 2-cyclopentenone (2) (5.0mM). The whole mixture was allowed to stand at room temperature for 1 hr. After quenching with saturated ammonium chloride (10mL), followed by the usual work-up, the resulting mixture was purified by column chromatography on silica gel to give only 1,4-adduct (3) in 68% yield (mp 75-76°C). When this reaction was quenched at -78°C without addition of HMPA, the yield of (3) was found to decrease slightly (53%) but 1,2-adduct could not be detected among the reaction products.

The reaction of the lithio derivative (1) with 2-cyclohexenone (4) smoothly occurred to provide 1,4-adduct (5) and 1,2-adduct (6). The product ratio depends on the reaction conditions. The results are summarized in Table 1.

![Diagram](image)

Table 1. Addition of 2-lithio-2-(2,6-dimethylpiperidino)acetonitrile to 2-cyclohexenone (4)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Additive (mol/mol of aminoacetonitrile)</th>
<th>Total yield (%)</th>
<th>1,4-Addition (5) %</th>
<th>1,2-Addition (6) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>240</td>
<td>HMPA (2.5)</td>
<td>72</td>
<td>37</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>-78</td>
<td>20</td>
<td>None</td>
<td>51</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>-78±25</td>
<td>60</td>
<td>HMPA (2.5)</td>
<td>70</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>-78±25</td>
<td>90</td>
<td>None</td>
<td>47</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>
The results shown in Table 1 indicate that the production ratio of 1,2- to 1,4-addition is obviously affected by the reaction temperature.\textsuperscript{6i,11} Namely, entries 1 and 2 should be compared with entries 3 and 4, where the product ratio of (5) and (6) was reverse in the reactions performed at -78°C and at room temperature. However, the presence of HMPA is effective for increasing the total yield and the ratio of the 1,4-addition product (entries 3 and 4). The solvent effect in this addition reaction is in marked contrast with the recent data\textsuperscript{6h} on the reactions of 2-lithio-1,3-dithians with cyclic 2-enones. We suggest that this reaction consists of a rapid reversible 1,2-addition followed by a slow 1,4-addition as illustrated in Scheme 1. In supporting this pathway, when a solution of the lithium salt of 1,2-adduct (6) in THF-HMPA was allowed to stand at room temperature for 1.5 hr, the conjugate addition product (5) (50%) was obtained.

\begin{center}
\begin{tabular}{c}
(6) \quad \leftrightarrow \quad \text{Li}^+ \quad \text{O} \quad \text{N} \quad \text{C}\n
\end{tabular}
\end{center}

Scheme 1

| (1) + (4) \rightarrow (5) |

\begin{center}
\begin{tabular}{c}
\text{-78°C} \quad \text{25°C} \quad \text{CN} \quad \text{O} \quad \text{Li}^+ \quad \text{CN}

\end{tabular}
\end{center}

Treatment of (-)-carvone (9) with the lithium salt (1) under the same conditions as shown in Table 1, entry 3 exclusively gave 1,4-adduct (10) in 60% yield.

\begin{center}
\begin{tabular}{c}
(9) \rightarrow (10)

\end{tabular}
\end{center}

Reduction of 1,4-adduct (5) with NaBH\textsubscript{4} in methanol gave the corresponding cyclohexanol derivative, which without further purification was subjected to hydrolysis with CuSO\textsubscript{4}·5H\textsubscript{2}O\textsuperscript{12} in refluxing methanol for 7 hr to afford hydroxy acetal (11) in 40% isolated yield.\textsuperscript{13}

\begin{center}
\begin{tabular}{c}
(5) \rightarrow (11)

\end{tabular}
\end{center}

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REFERENCES AND NOTES

4. Conversion of the -CH$_2$NO$_2$ group to CHO is performed by either an oxidative procedure (ref. 2d), a reductive method (ref. 2c), or a modified Nef reaction (ref. 2d). Diisobutylaluminium hydride has been used for transformation of the CN group to CHO (ref. 3).
7. The conditions required for the unmasking are not applicable to the unstable products. See ref. 6c.
10. 2-(2,6-Dimethylpiperidino)acetonitrile is readily prepared by the condensation of 2,6-dimethylpiperidine and chloroacetonitrile: F. Hoffmann-La Roche and Co., *Chem. Abstr.*, 2960h (1965).
13. When hydrolysis of α-aminoacetonitrile derivatives with CuSO$_4$·5H$_2$O in ethanol is carried out in a shorter reaction time (reflux, ca. 5min), the corresponding aldehydes are obtained. T. Wakamatsu, J. Kondo, S. Hobara, and Y. Ban, *Heterocycles*, 19, 481 (1982).

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