Facile Synthesis of Annelated NADH Model Precursors

R. Benoit, G. Dupas, J. Bourguignon,* G. Quignier

Laboratoire de Chimie Organique Fine et Hétérocyclique, INSA-IRCOF – BP 08, F-76130 Mont Saint Aignan, France

A convenient route to γ-cyano fused pyridine derivatives, which are precursors of NADH models, is described. The method involves the reaction of 3,3-dimethoxy-2-formyl-propionitrile sodium salt (I) with amino derivatives of electron donating heterocycles leading to the desired products by an easy one-pot synthesis.

NADH models such as 1,4-dihydrionicotinamide derivatives are widely used in organic synthesis because they are efficient chemo- and enantioselective reducing agents. They are generally obtained starting from pyridine precursors.

However the common models (for example, N-benzyl-1,4-dihydrionicotinamide: BNAH) can be affected by side-reactions which occur in the presence of traces of water on the 5,6-double bond of the dihydropyridine structure. These reactions can be minimized by annelation of this bond by an electrodonor ring in thieno-dihydrionicotinamide models which possess sufficient reactivity. Unfortunately the access to such compounds by reported methods is difficult and the yields are low.

It became apparent that in order to obtain easily large amounts of thieno[2,3-b]- or [3,2-b]-pyridines with a suitable substituent on the γ-position of the pyridine ring another method was needed. Moreover we could obtain other fused models when using amino derivatives of various aromatic compounds. Our planned strategy is represented in Scheme A.

\[
\begin{align*}
\text{Scheme A}
\end{align*}
\]
Table 1. Synthesis of Condensed Pyridines 3 from Amine 2 and 3,3-Dimethoxy-2-formyl-propionitrile Sodium Salt (I)

<table>
<thead>
<tr>
<th>Amine&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product 3</th>
<th>Reaction Time (h)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Molecular Formula or Lit. m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>3a</td>
<td>18</td>
<td>40</td>
<td>125</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;S (218.2)</td>
</tr>
<tr>
<td>2b</td>
<td>3b</td>
<td>24</td>
<td>75</td>
<td>123</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;S (160.2)</td>
</tr>
<tr>
<td>2c</td>
<td>3c</td>
<td>24</td>
<td>69</td>
<td>143</td>
<td>C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;S (175.2)</td>
</tr>
<tr>
<td>2d</td>
<td>3d</td>
<td>24</td>
<td>80</td>
<td>158</td>
<td>C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;S (210.3)</td>
</tr>
<tr>
<td>2e</td>
<td>3e</td>
<td>24</td>
<td>65</td>
<td>211</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (258.3)</td>
</tr>
<tr>
<td>2f</td>
<td>3f</td>
<td>24</td>
<td>85</td>
<td>143</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (172.2)</td>
</tr>
<tr>
<td>2g</td>
<td>3g</td>
<td>24</td>
<td>50</td>
<td>&gt;260</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (215.2)</td>
</tr>
<tr>
<td>2h</td>
<td>3h</td>
<td>24</td>
<td>76</td>
<td>93</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (172.2)</td>
</tr>
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</table>

<sup>a</sup> Amino derivatives are either commercially available (2h) or have been obtained by the following procedures:
2a, 2b, 2d, 2e: Reduction of the corresponding nitro derivatives with Sn + HCl;
2c, 2f, 2g: Prepared by literature methods.<sup>b,f,i</sup>

<sup>b</sup> Satisfactory microanalyses obtained: C ± 0.2, H ± 0.2, N ± 0.3.

The pyridine ring is built by a [3 + 3]-approach by using the following starting components:
- an amino derivative of the electron donor ring which provides the nitrogen and two carbon atoms of the pyridine;
- a synthon having the three other carbon atoms, namely two electrophilic atoms and a carbonyl (or equivalent) substituent on the middle carbon.

With respect to the described strategy and with the availability of commercial products we synthesized the 3,3-dimethoxy-2-formyl-propionitrile sodium salt (I) by a procedure similar to that described in the literature.<sup>5</sup> This synthon is more easily accessible than cyano malonaldehyde.<sup>6</sup>

![Scheme B](image)

Table 2. Spectral Data of Compounds 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR (KBr)&lt;sup&gt;a&lt;/sup&gt; (cm&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>1&lt;sup&gt;H&lt;/sup&gt;-NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;, TMS)&lt;sup&gt;b&lt;/sup&gt; δ, J(Hz)</th>
</tr>
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<tbody>
<tr>
<td>3a</td>
<td>2230, 1590</td>
<td>7.3 (1H, J&lt;sub&gt;4,5&lt;/sub&gt; = 6, H-23); 7.72 (1H, J&lt;sub&gt;1,2&lt;/sub&gt; = 5, H-2); 8.35 (1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-4); 8.78 (1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-6)</td>
</tr>
<tr>
<td>3b</td>
<td>2240, 1720, 1500</td>
<td>4.00 (s, 3H, OCH&lt;sub&gt;3&lt;/sub&gt;); 8.62 (s, 1H, H-2); 8.83 (1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-4); 9.13 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-6)</td>
</tr>
<tr>
<td>3c</td>
<td>2230, 1580</td>
<td>7.63 (1H, J&lt;sub&gt;1,2&lt;/sub&gt; = 6, H-2); 8.05 (1H, J&lt;sub&gt;1,2&lt;/sub&gt; = 6, H-2); 8.33 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-7); 8.90 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-5)</td>
</tr>
<tr>
<td>3d</td>
<td>3400, 3320, 2230, 1585</td>
<td>4.45 (m, 2H, NH&lt;sub&gt;2&lt;/sub&gt;); 6.82 (s, 1H, H-2); 8.38 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-7); 8.82 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-5)</td>
</tr>
<tr>
<td>3e</td>
<td>2235, 1590</td>
<td>7.53–8.25 (m, 4H&lt;sub&gt;meta&lt;/sub&gt;); 8.58 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-4); 8.87 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-2)</td>
</tr>
<tr>
<td>3f</td>
<td>2240, 1610</td>
<td>5.57 (s, 2H, CH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;); 7.37 (s, 5H, C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;); 7.90 (s, 1H, H-2); 8.35 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-4); 8.72 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-6)</td>
</tr>
<tr>
<td>3g</td>
<td>2240, 1615, 1715, 1635</td>
<td>2.67 (s, 3H, CH&lt;sub&gt;3&lt;/sub&gt;); 3.75 (s, 3H, OCH&lt;sub&gt;3&lt;/sub&gt;); 8.10 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-7); 8.60 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-5); 12.50 (m, 1H, NH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>3h</td>
<td>2240, 1615</td>
<td>5.53 (t, 1H, J = 7Hz, CH&lt;sub&gt;3&lt;/sub&gt;); 4.60 (q, 2H, J = 7, NCH&lt;sub&gt;2&lt;/sub&gt;); 8.13 (s, 1H, H-3); 8.38 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-4); 8.72 (d, 1H, J&lt;sub&gt;9a&lt;/sub&gt; = 2, H-6)</td>
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<sup>a</sup> Recorded on a Beckman IR 4250 spectrometer.
<sup>b</sup> Recorded on a Varian EM 360 L spectrometer.
<sup>c</sup> Measured in DMSO-d<sub>6</sub>, HMDS<sub>0</sub>. 
3,3-Dimethoxy-propionitrile is a commercial product having a cyano group which can easily be further converted into a carbamoyl substituent. The access to condensed \( \gamma \)-cyano pyridines is carried out as given in Scheme B. In the first step the crude enolate derivative 1 is suspended in methanol and exactly neutralized with hydrochloric acid. The solution is then treated with the amino derivative 2 for 4 hours at reflux. We assume that in this first step the condensation of the amine with the enol occurs. In the second step the mixture is then acidified by hydrochloric acid. The second formyl group is liberated from the acetal and the electrophilic substitution can occur leading to 3. The overall reaction is an easy one-pot formation of a pyridine ring fused to another heteroaromatic ring. The procedure is easier than that described for obtaining non-fused pyridine derivatives by using aminoacetonic esters and ethoxy carbonyl malonalddehyde (or its tosyl derivative). By this method we obtained eight products, seven of them being new compounds (Table 1).

In the case of 2d as starting material it must be noticed that it is the first example of a monocondensation on a 3,4-dimino-thiophene derivative.8

3,3-Dimethoxy-2-formyl-propionitrile Sodium Salt (1):
To a suspension of NaH (40% in oil in 3.0 g 0.063 mol) in dry ether (75 mL), is added 3,3-dimethoxy-propionitrile (6.25 mL, 0.055 mol, purchased from Janssen Company) and methyl formate (6.85 mL, 0.110 mol). The mixture is stirred at room temperature for 2 days under argon. The precipitate is then filtered, washed with ether and dried under vacuum. Yield: 7.75 g (86%).

The crude product is used without purification for the synthesis of pyridines 3.

5-Cyano-theno[2,3-b]pyridine (3a); Typical Procedure:
A solution of 2-aminoo-thiophene hexachlorostannane (2.7 g, 0.01 mol) in methanol (65 mL) is slowly added to a suspension of crude 3,3-dimethoxy-2-formyl propionitrile sodium and conc. HCl (1.3 mL) in methanol (20 mL). The mixture is gradually warmed to reflux for 4 h. A solution of conc. HCl (4 mL) in methanol (5 mL) is then added and the reflux continued for 12 h. After cooling, methanol is removed, water (25 mL) is added and the precipitate isolated by filtration and extraction in a Soxhlet apparatus with CH<sub>2</sub>Cl<sub>2</sub>. After removal of the solvent, the crude product is recrystallized from H<sub>2</sub>O/EtOH to give 3a; yield: 0.78 g (49%); m.p. 125°C (Table).

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Youn Kim, C.S., Chaykin, S. Biochemistry 1968, 7, 2339.