α-Aminonitriles as Versatile Building Blocks for the Synthesis of the Bisbenzylisoquinoline Skeleton of Tubocurarine

Nicola Otto and Till Opatz*

Johannes Gutenberg University of Mainz, Institute of Organic Chemistry, Duesbergweg 10–14, 55128 Mainz, Germany

Introduction

Benzylisoquinoline alkaloids constitute a family of more than 400 phenylalanine-derived metabolites sharing the structural motif of at least one diaryl ether linkage. Many of them were found to exhibit diverse biological activities such as antinflammatory, antibacterial, fungicidal and antitumor activities as well as antiepileptic effects which make these compounds attractive for pharmaceutical and agrochemical purposes. The most prominent example is tubocurarine (1), known as the arrow poison curare, which acts as a skeletal muscle relaxant by inhibiting the nicotinic acetylcholine receptor (2). Recently, we have shown α-aminonitriles to be useful building blocks for the modular enantioselective synthesis of dimeric benzyl tetrahydroisoquinolines. Here, we report on current studies towards the synthesis of the bisbenzylisoquinoline skeleton of tubocurarine from deprotonated α-aminonitriles.

Retrosynthetic Approach

The Chemistry of Deprotonated α-Aminonitriles

α-Aminonitriles bearing a hydrogen atom at the α-centre can be deprotonated resulting in the reversed polarity of α-amino-carbanions as compared to the electrophilic nature of the former iminium carbon. The resulting ketene imminium salts can undergo nucleophilic reactions such as 1,4-additions to β-unsaturated carboxyl compounds, alkylation, 1,2-additions to olefins, additions to aldehydes and epoxide ring openings.

In our group it was found that the use of strong bases devoid of Lewis-acidic cations such as KHMS allows the quantitative deprotonation of N-monosubstituted α-aminonitriles without risking the undesired retro-Streeker reaction. We used this methodology for the synthesis of a wide range of N-heterocycles as well as 1,2-aminoalcohols and 1,2-diamines.

Synthesis of α-Aminonitriles

Starting from 8-benzyl-protected vanillic 15, phenylalanine 17 has been synthesized by Henry-reaction and following reduction with LiAlH₄. Bischler-Napieralski reaction of the formamidine 17 or Petas-Strecker cyclization gives the imine 18 or the isoquinoline 19 respectively, which can be converted to the desired aminoiminonitrile 20 in two steps. The 3-bromo-substituted phenylalanine 26 is cleaved from the nitride 25 which can be synthesized from vanilline 14 in five steps.

Synthesis of Benzylbromides

TIPS-protection of 4-hydroxybenzaldehyde 29 and subsequent reduction gives benzylalcohol 30 which is converted to benzylbromide 31. The 3-iodobenzylbromide 32 can be obtained in five steps starting from p-toluenesulfonyl chloride 33. Reduction of 33 and subsequent ether cleavage gives aldehyde 34. Isolation of 4-hydroxybenzaldehyde can not be performed selectively and furnishes the halogenated products, which are not separable by chromatography or crystallization.

Synthesis of Benzylisoquinoline Building Blocks

The deprotonation of α-aminonitriles 10 and 11 with KHMS furnishes α-amino-carbanions which can be C-alkylated with the corresponding benzylbromides 31 and 32. Subsequent reduction with NaCNBH₄ yields the 1-benzyl 3,4-dihydroisoquinolines 34 and 35. The 8-benzyl-protected group of 9 is dehalogenated by hydrogenation to yield the corresponding benzylisoquinoline 34.

Ullmann Coupling Studies

Starting from two benzyl tetrahydroisoquinoline units 3a and 34, the seco-heterodimer 35 can be prepared by head-to-tail Ullmann coupling. Currently, different reaction conditions based on variation of metal salt and ligand as well as choice of base and solvent are investigated to optimize the 1st Ullmann coupling.

Conclusions & Outlook

The α-aminonitriles 10 and 11 have been successfully synthesized in 51% and 20% yield over seven and nine linear steps, respectively. Starting from the aminonitriles, the benzylisoquinoline building blocks 34 and 8a have been synthesized in 40% yield over nine linear steps and in 7% yield over ten linear steps. Currently, different reaction conditions for the 1st Ullmann coupling of the benzylisoquinolines 8a and 34 are investigated of which entry 4 (Table 1) shows potential for optimization. Furthermore, a stereoselective synthesis of the benzylisoquinolines 8 and 9 is in preparation.

Acknowledgments:

We thank Dr. J. C. Liermann (Mainz) for NMR spectroscopy and Dr. N. Hanold (Mainz) for mass spectrometry. The expert technical assistance by D. Kowalczyk (Mainz) is gratefully acknowledged. N. Otto is grateful for a PhD scholarship of the “Studienstiftung des deutschen Volkes”.

References:


Table 1: Reaction Conditions for 1st Ullmann Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal Source</th>
<th>Alcohol/nitrile</th>
<th>Base</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu/10 mol% DMF (40 mol%)</td>
<td>1.2:1</td>
<td>MeCN</td>
<td>K₂PO₃ (2.0 eq.)</td>
<td>80°C, 300 Watt</td>
<td>30 min</td>
</tr>
<tr>
<td>2</td>
<td>Cu (20 mol%)</td>
<td>1.2:1</td>
<td>MeCN</td>
<td>K₂PO₃ (2.0 eq.)</td>
<td>110°C, 300 Watt</td>
<td>5 h</td>
</tr>
<tr>
<td>3</td>
<td>Cu (10 mol%)</td>
<td>1:1</td>
<td>DMF</td>
<td>K₂PO₃ (2.0 eq.)</td>
<td>150°C</td>
<td>60 min</td>
</tr>
<tr>
<td>4</td>
<td>Cu (10 mol%)</td>
<td>1:1</td>
<td>pyridine</td>
<td>heating- reflux</td>
<td>20% —</td>
<td></td>
</tr>
</tbody>
</table>

α-HPLC-MS analysis, HPLC conversion H:zinc conversion, deoxidation, H:decomposition, H: not isolated.