The Effect of DMSO on the Borohydride Reduction of a Cyclohexanone: A Formal Enantioselective Synthesis of (+)-Epibatidine.

M. Teresa Barros, Christopher D. Maycock, and M. Rita Ventura

Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química, 2825 Monte da Caparica.

Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Rua da Quinta Grande 6, Apartado 127, 2780 Oeiras, Portugal

Received 2 July 1998; revised 30 October 1998; accepted 3 November 1998

Abstract: An asymmetric synthesis of (+)-epibatidine is described which uses the increased stereoselectivity of a borohydride reduction induced by the presence of DMSO. © 1998 Elsevier Science Ltd. All rights reserved.

(-)-Epibatidine 1 is an alkaloid isolated from the skin of the Ecuadorian poisonous frog *Epipedobates tricolor*, in 1992. Due to its low natural abundance (less than 1 mg obtained from 750 frogs), and to its strong non-opioid analgesic activity, greater than 200 times more potent than morphine and without addictive effects, it has stimulated many synthetic efforts. Several pharmacological studies have shown that epibatidine is a nicotinic acetylcholine receptor agonist, and these receptors are involved in several human disorders such as Alzheimer's and Parkinson's diseases. A bridged ring and the nature of the N-substituents are crucial to analgesic activity and interestingly (+) and (-) enantiomers of 1 are nearly equipotent in analgesic tests.

Here we report an expeditious enantioselective synthesis of (+)-epibatidine 2 starting from (-)-quinic acid (Scheme 1).

The enone 3 was readily available from quinic acid in three steps as described in the literature. Saturation using K-Selectride® followed by a base catalysed elimination of acetone produced the chiral enone 4 which was protected as the TBDMS ether 5. Using Johnson's method for the direct α-iodination of cyclic enones, (adding DMAP to accelerate the elimination of hydrogen iodide) we were able to obtain the iodo enone 6, in 82% yield.

The next step was the introduction of the 2-chloropyridinyl group. The necessary 2-chloro-5-pyridinyltributyltin reagent was synthesised from 2-aminopyridine in four steps. The iodine/lithium exchange reaction of 2-chloro-5-iodopyridine was carried out using t-butyllithium. Several reaction conditions were tested to obtain the cross-coupled product 7 from the vinyl iodide 6, using the Stille reaction. The effects of changing the palladium ligands and of added CuI on the rate of the reaction were studied. A large rate enhancement was observed with triphenylarsine as the palladium ligand, instead of triphenylphosphine, and the use of co-catalytic Cu(I) and Pd(0) species in this coupling was essential, since without CuI no reaction occurred. It has been reported that with soft palladium ligands like AsPh₃, the addition of CuI displayed little effect on the reaction.
rate, but with our system the presence of CuI was absolutely necessary. Johnson also used this combination in the particularly difficult Stille coupling of α-iodo enones.

Scheme 1: a) K-Selectride®, THF, -78°C. ii) NaOH 0.5 N, THF, 0°C. b) TBDMSCl, (i-Pr)2NEt, DMAP, CH2Cl2, 0°C/r.t. (51%, 3 steps). c) I2, DMAP, pyridine/CCl4 (1/1), 0°C/r.t., 82%. d) Bu3SnC5H3NCl, Pd2(dba)3.CHCl3, AsPh3, CuI, THF, r.t./60°C, 90%. e) K-Selectride®, THF, -78°C, 88%.

Chemoselective 1,4 reduction of the double bond of 7 was achieved with K-Selectride®, unfortunately we obtained the two epimers 8 and 9 in approximately a 1:1 ratio. Trost obtained some selectivity with a similar system, the only difference being a NHBoc group instead of the OTBDMS group in our example. In our case the two epimers 8 and 9 were very difficult to separate owing to their similar chromatographic mobilities, and we proceeded with the reduction of the carbonyl groups of this mixture (Table 1).

A range of reducing agents were tested on ketones 8 and 9, and some interesting conclusions could be reached. L-Selectride® gave only the two cis diastereoisomers 10 and 12, each having an axial hydroxyl. There were no significant differences between the ratios obtained with NaBH4 and NaBH4 with CeCl3.7H2O under similar reaction conditions. When we performed the reduction with NaBH4 in the presence of DMSO, however, the yield of the desired diastereoisomer 11 (m.p. 79-80 °C, [α]20°-10.6 (c 0.32 in CH2Cl2)) increased, and at -20 °C it was even better. However, simple borohydride reduction of this system at -20 °C afforded almost equivalent selectivities. Since the yield of the required diastereoisomer is higher than expected from the ratio of the ketones 8 and 9, we assume that 8 is being reduced more rapidly than 9 and that 9 is equilibrating with 8 via an enol under the reaction conditions. The reported reduction of a racemic analogue of 8, which was prepared via ozonolysis followed by reduction with Me2S then sodium borohydride, in a one pot procedure, gave similar and very high selectivity. We assumed that DMSO was present when the NaBH4 was later added to the unpurified product. Our assignment of the configurations to the various diastereoisomers produced was made by comparing their proton NMR spectra. The nature of this selectivity enhancement by DMSO is not understood. The major diastereoisomer obtained under these latter conditions 11 was that with the correct configuration for proceeding with our synthesis (Scheme 2).
Table 1: Reduction of the carbonyl group of a 1:1 mixture of epimers 8 and 9.

<table>
<thead>
<tr>
<th>Conditions/yield</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Selectride®, THF,-78 °C/50%</td>
<td>32%</td>
<td>0%</td>
<td>68%</td>
<td>0%</td>
</tr>
<tr>
<td>DIBAL-H, THF,-78 °C/67%</td>
<td>25%</td>
<td>20%</td>
<td>20%</td>
<td>35%</td>
</tr>
<tr>
<td>NaBH4, MeOH,0 °C/99%</td>
<td>31%</td>
<td>16%</td>
<td>16%</td>
<td>37%</td>
</tr>
<tr>
<td>NaBH4, CeCl3.7H2O, MeOH, 0°C/97%</td>
<td>25%</td>
<td>18%</td>
<td>13%</td>
<td>44%</td>
</tr>
<tr>
<td>NaBH4, DMSO (1 eq), MeOH,0 °C/79%</td>
<td>17%</td>
<td>49%</td>
<td>13%</td>
<td>21%</td>
</tr>
<tr>
<td>NaBH4, DMSO (2 eq), MeOH,0 °C/95%</td>
<td>11%</td>
<td>55%</td>
<td>9%</td>
<td>25%</td>
</tr>
<tr>
<td>NaBH4, MeOH, -20 °C/98%</td>
<td>8%</td>
<td>58%</td>
<td>10%</td>
<td>24%</td>
</tr>
<tr>
<td>NaBH4, DMSO (2 eq), MeOH, -20 °C/96%</td>
<td>8%</td>
<td>62%</td>
<td>4%</td>
<td>26%</td>
</tr>
</tbody>
</table>

In our analysis we assumed that the pyridine ring would control the conformation of the cyclohexane ring by always adopting an equatorial position, in spite of the bulky OTBS group. Thus, on one hand, we can clearly see that compounds with cis H-1 and H-2, 10 and 12, show a doublet signal for H-2, and the trans compounds 11 and 13 have a H-2 ddd signal. Compounds 10 and 11, both with the same chair conformation, have a lower field H-2 chemical shift than 12 and 13, which have the opposite chair conformation. The H-1 and H-4 coupling constants correlate well with the expected values for those between axial-equatorial, equatorial-equatorial and axial-axial protons in a chair conformer of cyclohexane.

Scheme 2: a) i) MsCl, Et3N, CH2Cl2, 0 °C, 99%. ii) Bu4NF, THF, r.t., 88%. b) PPh3, HN3, DEAD, THF, 0 °C/r.t., 94%.

Mesylation of 11 afforded the ester in quantitative yield, and without purification the TBDMS group was removed with Bu4NF to afford alcohol 14 (m.p. 108-109 °C, [α]D20 -45.0 (c 0.38 in CH2Cl2)) (Scheme 2). The conditions for this deprotection reaction were different from those of our previous experience with deprotection of silyl ethers in polyoxygenated molecules possessing an epoxy group, where traces of water were necessary. In this synthesis we had to perform the deprotection under strictly anhydrous conditions because if even a trace amount of water was present no desilylation was observed.
By applying the azide modification of the Mitsunobu reaction to compound 14, we obtained azide 15 with a small amount (5%) of an unsaturated byproduct, which was produced by elimination of the activated axial hydroxyl group under these reaction conditions. Azide 15 (m.p. 128-129 °C, [\(\alpha\])\(_D\)\(^{20}\) -10.1 (c 0.35 in CH\(_2\)Cl\(_2\))), after purification by recrystallisation, had a proton NMR spectrum which was identical with that previously reported. The conversion of the racemic form of azide 15 to epibatidine has already been reported in two syntheses.

In summary, an efficient asymmetric route has been developed for the synthesis of (+)-epibatidine 2 from readily available materials using mild reaction conditions. Our studies towards the enantioselective synthesis of (+)- and (-)-epibatidine by other routes are in progress.

Acknowledgment: We thank Fundação para a Ciência e a Tecnologia for a grant (Praxis XXI/BD/4527/94) conceded to M. R. V.

REFERENCES AND NOTES