ASYMMETRIC SYNTHESIS WITH CHIRAL HYDROGENOLYSABLE AMINES: A NEW ROUTE TO ENANTIOMERICALLY PURE AMINO DIOLS

Fabienne Segat, Olivier Lingibé, Bernadette Graffe, Marie-Claude Sacquet, and Gérard Lhommet*

Université P. et M. Curie, Laboratoire de Chimie des Hétérocycles, URA 408
4 Place Jussieu, F-75252 Paris Cedex 05 France

Abstract - Enantiomerically pure amino diols are obtained via diastereoselective reduction of chiral enamino and imino esters (3a), (3b), and (3c).

Chiral amino diols (7) constitute an interesting class of compounds used as asymmetric ligands\(^1,2\) or as intermediates in the synthesis of more complex molecules of biological interest.\(^3-8\) Ethanolamines (7a) (n=1) and (7b) (n=2) (Scheme I) can be prepared by reduction of (L)-aspartic and (L)-glutamic acid derivatives.\(^1,2,4,6\) However, the very limited scope of this route prompts us to develop a general method.

We report here a new route furnishing the amino diols of both R- and S-configurations (depending on the configuration of chiral inductor used) and amino diols with longer carbon chain (7) (n>2). So, our methodology constitutes an alternative access to the compounds (7c) and ent-(7a,b,c) otherwise obtained by reduction of expensive amino diacids. Moreover, this method could provide longer amino diols (7) (4≤n≤8) for which the corresponding amino diacid derivatives are not commercially available.

This route requires phenylglycine (12) as chiral auxiliary for which both enantiomers are commercially available and inexpensive. The key step, involving the chiral induction, is the diastereoselective reduction of the cyclic enamino and imino esters (3a,b,c).

We have previously described high yielded preparation of chiral oxazinones (3b,c) from the chloro keto esters (1b,c) and potassium R-N-(benzyloxy carbonyl)phenylglycinate.\(^9,10\) When we applied the same reaction to the commercially available chloro keto ester (1a), the substitution product (2a) is obtained in moderate yield (65%) whereas the homologous amino keto esters (2b,c) were isolated in excellent yields.\(^9\)
This can be explained by the high reactivity of compound (1a) bearing both a nucleophilic site (malonic type methylene group) and an electrophilic site (α-chloromethylene group). Thus, dimerization of 1a competes with the substitution.11

Scheme I

\[
\begin{align*}
\text{X} & = \text{Cl} \\
\text{X} & = \text{OCOCH(NHZ)Ph} & \text{R}
\end{align*}
\]

i) \(-\text{R-PhCH(NHZ)CO}_2\text{K, DMF or CH}_3\text{CN, rt.}\)

ii) \(-\text{HBr/CH}_3\text{CO}_2\text{H ; K}_2\text{CO}_3\text{ powder.}\)

iii) \(-\text{Reduction (Table I); chromatographic separation.}\)

iv) \(-\text{LiAlH}_4, \text{THF, rt, 5 h.}\)

v) \(-\text{H}_2, 1 \text{ atm, 10\% Pd/C, refluxing CH}_3\text{OH, 4 h.}\)

The cyclisation of the amino ketone (2a) takes place under similar conditions to those described for products (2b,c)\(^9\) (HBr/AcOH then solid K\(_2\)CO\(_3\)). The enamino ester (3a) (95 % of crude product), carrying
an exocyclic carbon-carbon double bond conjugated with the nitrogen atom and the ester function, is obtained while the cyclisation of the amino ketones (2b) (n=2) and (2c) (n=3) lead to imino esters (3b,c) with an endocyclic carbon-nitrogen double bond. Only the Z-isomer of the compound (3a) is formed as it is highly stabilized by an intramolecular hydrogen bond between the hydrogen on the nitrogen atom and the ester carbonyl function.¹²

The diastereoselective reduction of 3a was then studied and the results are summarized in Table I.

Table I: Reduction of 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound (3)</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Time a</th>
<th>Yield of 5 (%) b</th>
<th>5 / 4 c cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>BH₃, THF (1.4 eq)</td>
<td>CH₃CN</td>
<td>6 h</td>
<td>trace d</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>NaBH(OAc)₃ (1.6 eq)</td>
<td>THF or CH₃CN</td>
<td>7 h</td>
<td>26 e</td>
<td>70 / 30</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>10% Pd/C</td>
<td>CH₃OH</td>
<td>6 h</td>
<td>f</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>PtO₂</td>
<td>CH₃OH</td>
<td>6 h</td>
<td>18 g</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>10% Pt/C</td>
<td>THF or CH₃CO₂CH₃</td>
<td>14 to 41 h b</td>
<td>23</td>
<td>97 / 3</td>
</tr>
<tr>
<td>6</td>
<td>3b</td>
<td>10% Pd/C</td>
<td>CH₃OH</td>
<td>5 h</td>
<td>77</td>
<td>87 / 13</td>
</tr>
<tr>
<td>7</td>
<td>3b</td>
<td>PtO₂</td>
<td>CH₃OH</td>
<td>4 h</td>
<td>73</td>
<td>85 / 15</td>
</tr>
</tbody>
</table>

(a)- All the reactions were performed at rt.
(b)- Chromatographed products. Yields refer to materials purified by column chromatography.
(c)- Determined by ¹H-NMR analysis of the crude products.
(d)- Starting material was also recovered. When more excess reagent (2.5 eq) was used, complete decomposition of the starting material occurs in 2 h.
(e)- The products (4a) and (5a) were accompanied by side-product (13) (N-acetylation then amide reduction).
(f)- Starting material and phenylglycine (12) were obtained from the crude product.
(g)- Methanolation and hydrogenolysis side-products (10) and (11) were also recovered from the crude.
(h)- Time is depending on the catalyst origin. The reaction must be monitored by ¹H-NMR to follow the starting material consumption.

The chemical reduction conditions previously established for the imino esters (3b,c)⁹ are applied to the enamino ester (3a) (Entries 1, 2). Unfortunately, the desired oxazinones (4a) and (5a) are not obtained in a satisfactory manner. So, we have developed catalytic reduction (Pd/C or PtO₂ in methanol) giving good results for 3b (Entries 6, 7). When we extended these conditions to 3a (Entries 3, 4), the desired products (4a) and (5a) are either not formed or isolated in low yield because undesirable methanolation and
hydrogenolysis products (10), (11) and phenylglycine (12) are also obtained (Scheme II). The most suitable reduction method was direct hydrogenation using 10% Pt/C (Entry 5). In these conditions, excellent diastereoselectivity was observed (d.e. = 94 %) although 4a and 5a are formed in low yield again due to hydrogenolysis side-product (11). So, the enamino ester (3a) proved to be far more resistant to reduction than its homologues (3b,c). In agreement with this observation, it is interesting to note that the enamino ester (3a) is more stable than the imino esters (3b,c) which had to be reduced rapidly otherwise they decomposed. The lower reactivity of 3a towards reducing agents is due to its higher stability as it is a conjugated system.

After chromatographic separation of the two diastereoisomers (4) and (5), the major cis-oxazinones (5) were easily reduced (LiAlH$_4$ in THF) into amino triols (6) ((6a) : 73% ; (6b) : 69% ; (6c) : 74%). These amino triols were then hydrogenolized over 10% Pd/C in refluxing methanol$^{13}$ and lead to the oily S-amino diols (7) in good yields (Table II). These amino diols were unambiguously characterized by their $^1$H and $^{13}$C-NMR spectra.

Table II : Amino diols (7)

<table>
<thead>
<tr>
<th>Amino diols (7)</th>
<th>Yield (%)</th>
<th>$[\alpha]_D^{20}$</th>
<th>c</th>
<th>Solvent</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>71</td>
<td>+4.1</td>
<td>1.85</td>
<td>CH$_3$CO$_2$H</td>
<td>5, 14</td>
</tr>
<tr>
<td>7b</td>
<td>76</td>
<td>-1.9</td>
<td>1.97</td>
<td>CH$_3$OH</td>
<td>14</td>
</tr>
<tr>
<td>7c</td>
<td>88</td>
<td>+14.7</td>
<td>1.00</td>
<td>C$_2$H$_5$OH</td>
<td>---</td>
</tr>
</tbody>
</table>

In summary, we achieved the synthesis of enantiomerically pure amino diols (7) with both S- and R-configurations, which could be prepared by reduction of the corresponding amino diacid derivatives of prohibitive price. Moreover, our methodology could provide amino diols having longer carbon chain. Indeed, homologous chloro keto esters (1) ($4 \leq n \leq 8$) can be prepared from corresponding commercially available anhydrides or chloro acids according to the method previously described.$^9$

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REFERENCES AND NOTES

11. Unreacted amino acid (8) and side-product (9) were isolated from the mixture of the crude products.
   Compound 9 may arise from the acido-basic equilibrium followed by anionic condensation:

\[
\begin{align*}
\text{PH}^{+} &\text{CO}_{2}\text{K} + \text{Cl} &\text{CO}_{2}\text{H} + \text{Cl} &\text{NHZ} + \text{OCH}_{3} \\
\text{Cl} &\text{CO}_{2}\text{H} + \text{Cl} &\text{K} &\text{OCH}_{3} \\
\text{CH}_{2} &\text{O} &\text{C} &\text{CO}_{2}\text{CH}_{3}
\end{align*}
\]

13. This debenzylation did not occur at room temperature under H₂ (1 atm or 180 atm).
14. [α]D of 7a and 7b are identical to those of amino alcohols obtained by reduction of L-aspartic and L-glutamic acids.

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