Steroselective Synthesis of Imidazolidin-4-ones from α-Amino Amides of the Antimalarial Primaquine and Substituted Benzaldehydes

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Imidazolidin-4-ones are commonly employed as skeletal modifications in bioactive oligopeptides, either as proline surrogates or for protection of the N-terminal amino acid against aminopeptidase-catalysed hydrolysis\textsuperscript{1}. We have been working on the synthesis of imidazolidin-4-ones of the antimalarial primaquine\textsuperscript{2}, through acylation of primaquine with an α-amino acid and subsequent reaction of the resulting α-aminoamide with a ketone or aldehyde. Thus, when using racemic primaquine, an optically pure chiral α-amino acid and an aldehyde as starting materials, four imidazolidin-4-one diastereomers are to be expected (Scheme 1). However, we have recently observed that imidazolidin-4-one synthesis was stereoselective when 2-carboxybenzaldehyde (2CBA)\textsuperscript{\textdagger} was used, as only two diastereomers were produced\textsuperscript{2}. Computational studies have shown that the imine formed prior to ring closure had, for structures derived from 2CBA, a quasi-cyclic rigid structure\textsuperscript{2}. This rigid conformation is stabilized by an intramolecular hydrogen bond involving the C=O oxygen atom of the 2-carboxyl substituent in 2CBA and the N-H group of the α-aminoamide moiety\textsuperscript{2}. These findings led us to postulate that the 2-carbonyl substituent in the benzaldehyde moiety was the key for the stereoselective synthesis of the imidazolidin-4-ones\textsuperscript{2}.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{MeO} \begin{array}{c} \text{N} \\
\text{HN} \end{array} \begin{array}{c} \text{CH}_3 \\
\text{NH}_2 \end{array}}; \node (b) at (2,0) {\text{MeO} \begin{array}{c} \text{N} \\
\text{HN} \end{array} \begin{array}{c} \text{CH}_3 \\
\text{NH}_2 \end{array}}; \node (c) at (4,0) {\text{MeO} \begin{array}{c} \text{N} \\
\text{HN} \end{array} \begin{array}{c} \text{R}_1 \\
\text{R}_2 \end{array}};
\node (d) at (0,-1) {\text{MeO} \begin{array}{c} \text{N} \\
\text{HN} \end{array} \begin{array}{c} \text{CH}_3 \\
\text{NH}_2 \end{array}}; \node (e) at (2,-1) {\text{MeO} \begin{array}{c} \text{N} \\
\text{HN} \end{array} \begin{array}{c} \text{CH}_3 \\
\text{NH}_2 \end{array}}; \node (f) at (4,-1) {\text{MeO} \begin{array}{c} \text{N} \\
\text{HN} \end{array} \begin{array}{c} \text{R}_1 \\
\text{R}_2 \end{array}};
\draw[->] (a) -- (b) node[midway, above] {\text{(i)}}; \draw[->] (b) -- (c) node[midway, above] {\text{(ii)}}; \draw[->] (d) -- (e) node[midway, above] {\text{(iii)}}; \draw[->] (e) -- (f) node[midway, above] {\text{(i)}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1} – General synthetic route for imidazolidin-4-ones of primaquine: (i) DCCI, HOBt, N\textsuperscript{\textdagger}-BocAAOH; (ii) TFA, Na\textsubscript{2}CO\textsubscript{3}; (iii) substituted benzaldehyde in refluxing methanol, TEA, molecular sieves.

\textsuperscript{\textdagger} the non-IUPAC name “2-carboxybenzaldehyde” was chosen instead of “2-formyl-benzoic acid”, so that the aldehyde functionality, which is involved in the reactions under study, could be emphasized.