Synthesis and applications of unsaturated non-proteinogenic a-H-a-amino acids.

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SUMMARY

SYNTHESIS AND APPLICATIONS OF UNSATURATED NON-PROTEINOGENIC \( \alpha \)-H-\( \alpha \) AMINO ACIDS

In recent years, the use of both racemic and enantiomerically pure non-proteinogenic amino acids has – in addition to the use of naturally occurring amino acids – become increasingly important in synthetic routes. Due to the additional variety of functional groups in the side chains, new applications were developed in chemistry, biology and material science. This thesis focuses on the synthesis of a series of enantiopure unsaturated amino acids (Scheme 1) and on investigations towards synthetic applications of the acetylene- and allene-containing amino acids.

Scheme 1

\[
\begin{align*}
1 & : \quad \text{H}_2\text{N} - \text{CO}_2\text{H} \\
2 & : \quad \text{H}_2\text{N} - \text{CO}_2\text{H} \\
3 & : \quad \text{H}_2\text{N} - \text{CO}_2\text{H} \\
\text{n} & = 1, 2, 3 \quad \text{R} = \text{H}, \text{Me}
\end{align*}
\]

In Chapter 1, an overview of recent applications of such amino acids in organic chemistry, biology and material science is presented.

Chapters 2 and 3 deal with the synthesis of the amino acids 1-3 in enantiopure form. In Chapter 2, the synthesis of the racemic amino acid amides is described, which either involves alkylation of glycine derivative 6 with the appropriate unsaturated halide (eq 1) or a modified Strecker reaction eventually starting from an unsaturated alcohol (viz. 9) (eq 2).

\[
\begin{align*}
\text{4} & \quad \text{H}_3\text{N}^+\text{CONH}_2^- \\
\text{7} & \quad \text{H}_3\text{N}^+\text{CONH}_2^- \\
\text{5} & \quad \text{Ph}^-\text{N}^-\text{CONH}_2^- \\
\text{8} & \quad \text{H}_2\text{N}^-\text{CN}^- \\
\text{6} & \quad \text{Ph}^-\text{N}^-\text{CONH}_2^- \\
\text{9} & \quad \text{CH}_3\text{CH}_2\text{OH}^- \\
\end{align*}
\]
Both synthetic routes proved to be efficient (overall yields around 50%) containing only a single purification step (crystallization from acetone) at the end of the procedure. Therefore, these routes can be readily applied in a large scale synthesis.

Chapter 3 describes the enzymatic kinetic resolution of the racemic amino acid amides to the enantiopure (S)- and (R)-amino acids. An example is shown in Scheme 2 using the racemic amino acid amide 9.

An aminopeptidase present in the whole cells of Pseudomonas putida ATCC 12633 was used as the biocatalyst. The resolutions were also carried out using a genetically modified organism (GMO), i.e. an E. coli DH5α/pTrpLAP host micro-organism in which the gene coding for the aminopeptidase was brought to overexpression. The latter system appeared superior in the resolution experiments. It was shown that the cells of P. putida contained an amino acid racemase, which was not observed in the GMO cells. This amino acid racemase appeared to display narrow substrate specificity for methionine and structurally and electronically related compounds such as 11.

Pd-catalyzed cyclization reactions using acetylene-containing amino acids 2 (n = 1, 2; R = H) and the corresponding amino alcohols are detailed in Chapter 4. An example of these types of reactions, which entails the formation of an enantiopure proline-derivative via a cyclization/cross-coupling-reaction is shown in eq 3. Cyclization reactions using the carboxylic acid moiety as the nucleophile gave similar types of ring closure reactions leading to the corresponding lactones.
In Chapter 5, Pd-catalyzed reactions with allene-containing amino acids 3 are described. By varying the protecting group on the nitrogen atom and the reaction conditions, four- and/or six-membered rings were formed in a selective manner. As an example, the cyclization of allene 15 (eq 4) provided compounds 16 and 17 in ratios ranging from 88:12 (THF, 60 °C, 1.5 h) to 0:100 (DMF, 80 °C, 4 h).

Finally, Chapter 6 details the synthesis of cystine analogues using the acetylene-containing amino acids 2 (n = 1-3, R = Me). In this route, two amino acid residues were coupled using a suitable linker molecule (viz. 18, eq 5) and cyclized via ring-closing alkyne metathesis under the influence of a W-alkylidyne catalyst (19). Hydrolysis of the ester moieties and subsequent deprotection of the amino groups afforded the cystine analogue 20. Furthermore, this pathway provided access to the corresponding (Z)-olefin and the saturated derivative via (partial) hydrogenation. In addition, orthogonally protected diamino dicarboxylic acids are accessible via a slight adaptation of the strategy.