Amino-acid like subunits based on iminodiacetic acid and their application in linear and DKP libraries

P. Safár, A. Stierandová and M. Lebl

Selectide Corporation, 1580 E. Hanley Blvd., Tucson, AZ 85737, U.S.A.

Introduction

The preparation and use of synthetic combinatorial libraries (peptidic or non-peptidic) and multiple synthesis has received much attention recently, since this approach provides a collection of compounds suitable for both drug discovery and drug development [1,2]. The utility of peptide libraries is limited by the physico-chemical properties of the peptides generated, their metabolic stability, and bioavailability. One solution to these problems is the use of unnatural amino acids as subunits, *e.g.* N-substituted glycines described earlier [3]. We have explored the use of iminodiacetic acid (Ida) and its derivatives as a basis for the synthesis of linear and DKP-based libraries and structures.

Results and Discussion

We used Ida for both the backbone and side chain modification as depicted in Fig. 1. Protected monomers can be synthesized by opening the anhydride by an amine and used in solid phase synthesis. For the coupling to a secondary amine, PyBrop [4] or symmetrical anhydrides have to be used. An alternative synthesis of Ida-oligomers is based on opening the protected cyclic anhydride by a resin bound amine and modifying of the generated carboxy group with a variety of amines.

Monoesters or 'activated' amides (*e.g. p*-nitroanilide) of Ida acylated by an α-amino acid can be used for synthesis of a disubstituted N-terminal DKP-ring. The DKP-closure proceeds quantitatively during the Fmoc-deprotection extended up to 1 h (Fig. 2). Using the *p*-nitroanilide, the progress and completeness of the DKP-closure can be quantitatively monitored at 382 nm. For library synthesis, the more reactive and easily accessible protected Ida-monomethyl ester was used.

Identification of compounds from the library was accomplished by Edman degradation of a coding structure built in parallel by the coupling of a 7:3 mixture of Fmoc-Ida(OMe)-OH and Fmoc-Gly-OH. For DKP-closure, an array of α-amino acids (N-substituted, cyclic, α-substituted) can be used.

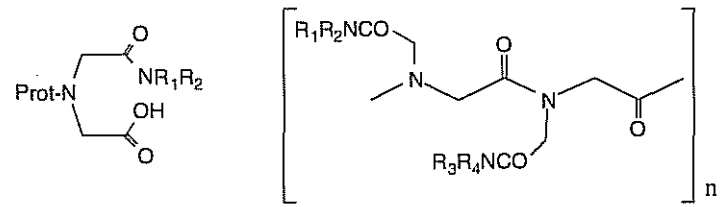

Fig. 1. Protected Ida-monomers and general structure of the oligomer.

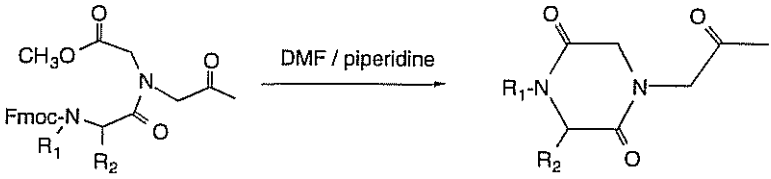

Fig. 2. DKP-structure.

Conclusions

Protected monoamides of iminodiacetic acid can be used to increase the diversity of compounds that can be produced by library synthesis. Two disadvantages connected with their use are the analysis (two pathways of Edman degradation) and the stringent conditions necessary for coupling (PyBrop or symmetrical anhydrides).

The first disadvantage can be overcome by a coding. The DKP-structures described can be easily synthesized in a library format or as single compounds.

References

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