Peptide Revolution: Genomics, Proteomics & Therapeutics
Michael Chorev & Tomi K.Sawyer (Editors)
American Peptide Society, 2003

Dialkyl Imidazolinones from α,α-Dialkyl Glycines

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Introduction

Peptides containing residues of α,α-dialkyl glycines are known since the 1960s and lately have been widely used in modification of natural peptides and in peptidomimetics [1]. Nevertheless, most of the reports found in literature refer to the simplest representative of this class of compounds, i.e. α,α-dimethyl glycine (Aib), which is certainly due to the discouraging difficulties usually met during syntheses. In fact, usually α,α-dialkyl glycines are not readily available compounds, their synthesis being most commonly carried out by hydrolysis of specially prepared hydantoins or Schiff bases, but, owing to steric crowding, these reactions are slow and lead almost always to low yields. Furthermore, most methods of peptide synthesis are of little use to handle these compounds [2].

Ugi's four-component condensation reaction is known to be a complement or even an alternative to classical peptide synthesis but one can hardly find any such application in literature. This is due to two inherent drawbacks: (i) peptide isonitriles, required for the reaction, racemise above –20ºC and (ii) an unavoidable *N*-alkyl group needs to be cleaved from the reaction product [3]. In recent years, we have been involved in a study of the application of Ugi's reaction to the synthesis of several α,α-dialkylglycines. Using 4-methoxybenzylamine (Pmb-NH_2) as the amine component, we were able to remove the *N*-alkyl group by TFA cleavage and, during this process, the *C*-terminal amide bond of the resulting Ugi adducts was cleaved by a mechanism involving an oxazolinium-type intermediate (see Figure 1) [4]. This intermediate allows *in situ* functionalization of the C-terminus by reaction with several nucleophiles (HO^-, MeO^- and amines), thus affording different derivatives such as free acids, esters and amides [5].

We now report, the results obtained so far in the attempt of *in situ* formation of peptide bonds.

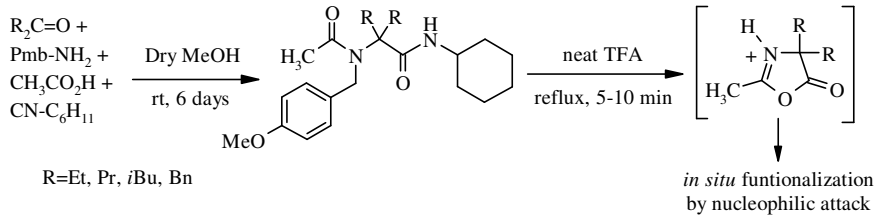

Fig. 1. Schematic representation of the intermediate formed during TFA cleavage of Ugi adducts

Results and Discussion

Our previous findings suggested that a dipeptide could be obtained if an amino acid ester was used as the nucleophile. We started out by the usual treatment of the Ugi reaction product (diethyl and dibenzyl glycine derivatives) with neat TFA in order to obtain the corresponding oxazolinium intermediates. After removal of excess TFA, a solution with 2 eq of glycine *tert*-butyl ester and 3 eq of NEt_3 was added to the residue.

Although a small amount the required dipeptides (2) (<15% yield) was formed, the major products were 5,5-dialkyl-imidazolin-4-ones (1) (>75% yield) (see Figure 2), resulting from competitive attack at the less hindered C-2 of the oxazolinium intermediate, followed by rearrangement. Furthermore, the presence of a positive charge at the oxazolinium nitrogen atom renders the adjacent carbon more prone to nucleophilic attack than that at the carbonyl group.

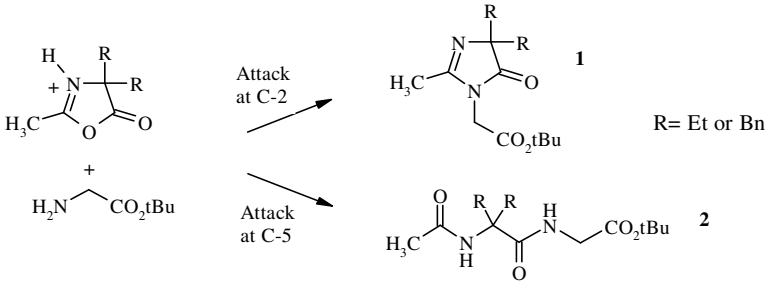

Fig. 2. Schematic representation of competitive nucleophilic attack at the oxazolinium salt.

Then, we decided to neutralize the oxazolinium salt by adding 20 eq of NEt_3 in acetonitrile to the residue obtained after TFA evaporation, so that the coupling reaction could proceed via the corresponding oxazolone by nucleophilic attack at C-5. Although some imidazolinone was still obtained, we were able to improve dipeptide formation (83 and 49% yield for diethyl and dibenzyl glycine dipeptide, respectively).

These results, combined with previous findings [5], suggest that the bulkiness of the nucleophile and α-alkyl groups and the positive charge at N-3, directs nucleophilic attack either to C-2 or C-5. Therefore, *in situ* formation of peptide bonds can be accomplished; however reaction conditions have to be carefully controlled.

References

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