An improved approach to the synthesis of *N*-acyl-α,α-dialkylglycines, their esters and amides using Ugi's four-component reaction

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Introduction

Owing to steric hindrance, synthesis of and reactions with α,α-dialkylglycines are very slow; thus, most methods of peptide synthesis are of little use to handle these compounds when the α-alkyl groups are larger than methyl. Ugi's four-component reaction is appropriate to synthesise these amino acids [1], but for peptide synthesis it presents two drawbacks, *i.e.* (*i*) peptide isonitriles racemise above –20 ºC and (*ii*) an unavoidable *N*-alkyl group needs to be cleaved from the reaction product [2].

The former could be avoided by cleaving selectively the amide bond at the C-terminus of the Ugi adduct to allow making the peptide chain grow in this direction and this can be achieved by taking advantage of the use of some isonitriles that have been devised specially for this purpose [3]. As reactions involving α,α-dialkylglycine derivatives are usually too slow to allow the use of low temperatures, this is the only strategy appropriate to deal with these compounds; however, no special isonitriles are required, as in this case the amide bond generated by any isonitrile is already sufficiently labile to acid to allow its mild cleavage [4,5]. By using 4-methoxybenzylamine, which yields a TFA labile *N*-alkyl group in the Ugi adduct [4], we have been able not only to overcome the latter difficulty but also to cleave simultaneously the amide bond at the C-terminus. In addition to this combined strategy and having in mind that cleavage of the amide seemed to proceed through a *5*(*4*H)-oxazolonium-type intermediate [3-5], we have developed an improved method for *in situ* functionalisation of the amino acid C-terminus.

Results and Discussion

Acetic acid, 4-methoxybenzylamine, dibenzylketone and cyclohexyl isonitrile were reacted in dry methanol to give Ac-Db_zg(*N*-MeOBzl)-NHC_6H_{11} with a yield of 73%. After purification, the product was cleaved by treatment with neat TFA under reflux for 5-10 minutes (Fig. 1). The excess TFA was then removed in a rotary evaporator and the residue reacted with a nucleophile to give different products depending on the nature of the latter reagent.

Thus, the *N*-acetyl amino acid (Ac-Db_zg-OH) was isolated in a yield of 89% by treatment with an aqueous solution of NaOH. The product was converted into the corresponding *5*(*4*H)-oxazolone by the DCC method, which was then coupled with ciclohexylamine to give Ac-Db_zg-NHC_6H_{11} in a yield of 41%, or with glycine *tert*-butyl ester to yield 43% of the expected dipeptide, Ac-Db_zg-Gly-O*t*Bu.

The use of a methanolic solution of sodium methoxide, instead of aqueous NaOH, lead to the *N*-acetyl amino acid methyl ester in a yield of 60%.

Reaction with amines seems to be very slow, but the use of neat benzylamine gave a yield of 51% of the corresponding amide. Reaction of the crude residue, as obtained from the TFA treatment, with a solution of glycine *tert*-butyl ester in dry acetonitrile required reflux for two days and previous neutralisation with triethylamine to remove any traces of TFA. The expected Ac-Db_zg-Gly-O*t*Bu was isolated in a yield of 20%. We are now making efforts to improve this result, although it is well known that, owing to the poor reactivity of these compounds, their reactions tend to give only moderate to low yields.

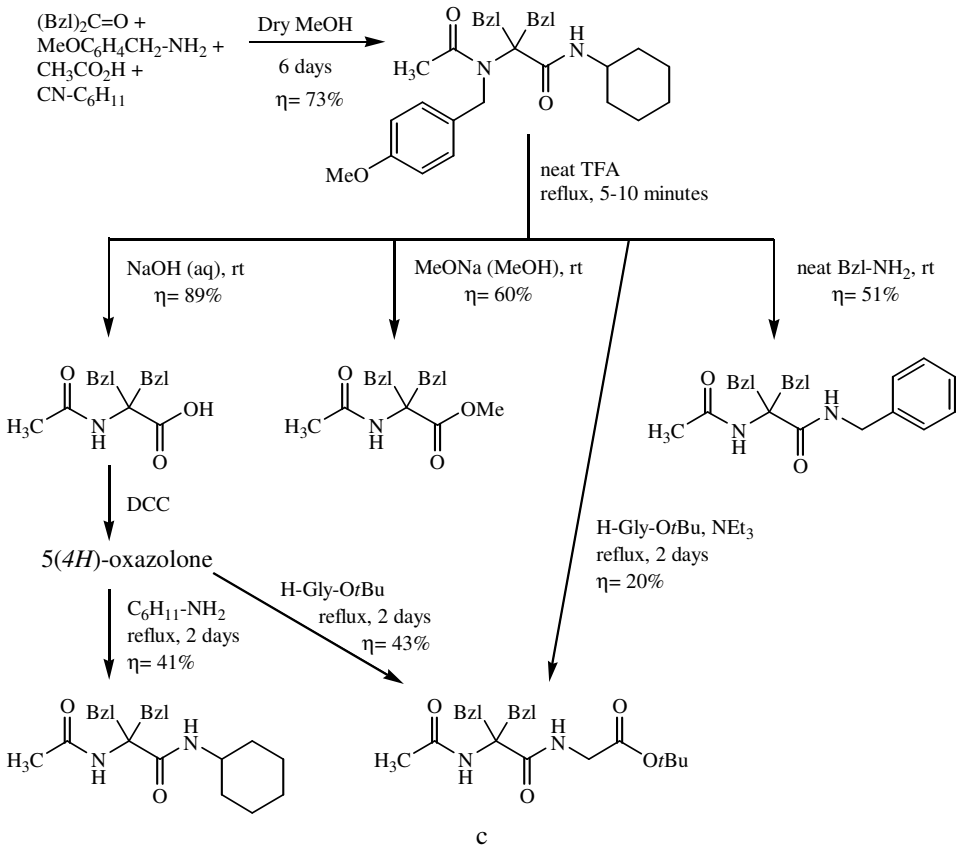

Fig. 1. Representation of the reactions leading to different derivatives of Ac-Db$_z$g-OH.

So far, as shown in Fig. 1, the same dipeptide could be obtained with a better overall yield (38%) but in a two-step approach *via* the 5(4H)-oxazolone.

Similar results were obtained for other α,α-dialkylglycines related to the above, *viz.* Deg, Dpg and D$_i$bg.

These results are in agreement with the formation of an intermediate 5(4H)-oxazolonium salt as previously proposed for the mechanism of cleavage of the C-terminal amide bond [3-5].

References

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