C-Terminal Amide Bond Stability of Peptides Containing $C^{\alpha,\alpha}$-Disubstituted Glycines

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Introduction

The Ugi-Passerini Four Component Condensation Reaction showed to be most appropriate to prepare amino acid derivatives with a crowded α-carbon atom, but (*i*) the alkyl group generated at its nitrogen atom and (*ii*) the tendency that amino acid isonitriles show to racemize have prevented the use of this reaction for routine synthesis of peptides. However, these facts did not diminish its usefulness for amino acid synthesis.

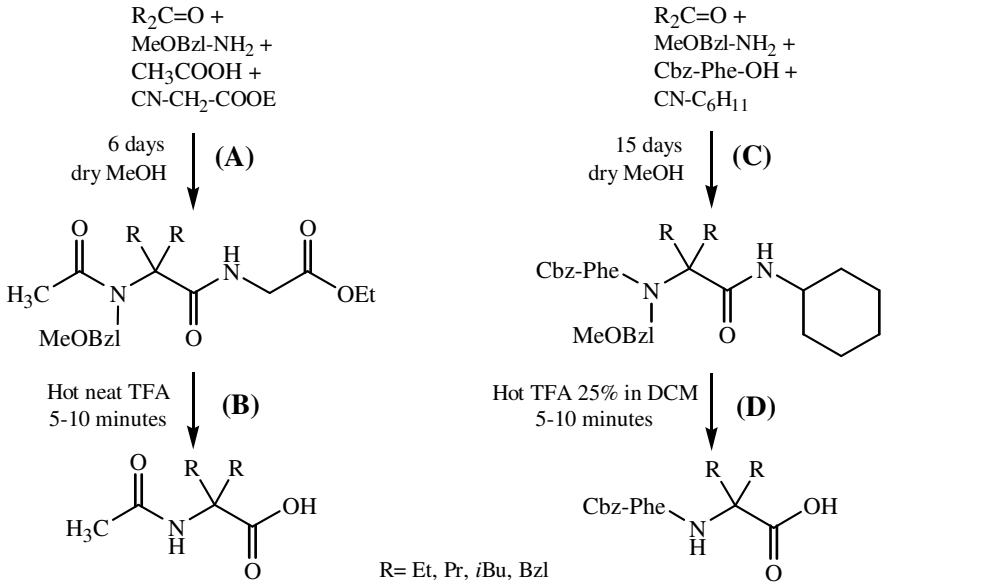
We have since long been interested in the synthesis of $C^{\alpha,\alpha}$-disubstituted glycines using this reaction [1] and recently have improved our previous method by using 4-methoxybenzyl amine as the amine component of the reaction, which allowed an important simplification in the subsequent deprotection of the product. During cleavage of the 4-methoxybenzyl group with hot neat TFA, we detected, like other authors [2], that not only this group was removed but also the C-terminal amide bond was cleaved. This result was independent of the nature of both the amino acid residue generated and the *N*-substituent at the C-terminal amide group [3].

Results and Discussion

In previous work, we have shown that for *N*-acetyl and *N*-(4-methoxybenzyl) amides of Deg, Dpg and D_ibg, when HCl or TFA (either neat or 2% in acetonitrile) was used at room temperature, only the C-terminal amide bond was cleaved, while removal of the 4-methoxybenzyl group required neat TFA in much longer reactions or at higher temperatures. In the case of the Db_2g the behaviour was similar, but no selectivity was observed in neat TFA at room temperature, which suggests that in this case the rate of cleavage of the amide bond is similar to that of the *N*-alkyl group [3].

These findings were then applied to a series of dipeptide derivatives of the same $C^{\alpha,\alpha}$-disubstituted glycines that were synthesised by the Ugi-Passerini reaction. In the preparation (A) of dipeptides having Gly-OEt at their C-terminus the lower yields observed might be due to decomposition of the isonitrile during the reaction. In the presence of TFA these peptides behaved (B) like the previously studied amino acid amides, leading us to the conclusion that whenever an *N*-alkyl $C^{\alpha,\alpha}$-disubstituted glycine is present in a peptide, the peptide bond at the C-terminus of this residue is extremely sensitive to TFA.

When a *N*-Cbz amino acid was used as the acid component in the Ugi-Passerini reaction (C), fully protected dipeptides were obtained in good yields. By controlling the conditions of the subsequent reaction with TFA, we were able to obtain (D) the *N*-Cbz protected dipeptides. These can be readily used in oxazolinone couplings [1] in routine peptide synthesis, thus avoiding the main difficulties usually encountered during synthesis of peptides containing $C^{\alpha,\alpha}$-disubstituted glycines.



Scheme 1. *Preparation of dipeptides by the Ugi-Passerini Reaction and their deprotection with TFA.*

Table 1. *Yields of isolated, purified products of the reactions on Scheme1.*

R	Yields / %			
	A	B	C	D
Et	59	86	88	88
Pr	51	91	82	86
*i*Bu	48	78	70	85
Bzl	41	81	60	69

References

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3. a) Results presented at the 16th APS, poster P022, Minneapolis, Minnesota, USA, July, 1999. b) Results presented at the VII EPI, oral presentation I-2, Valencia, Spain, February, 2000.