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Synthesis of *gem*-diamino derivatives on solid support

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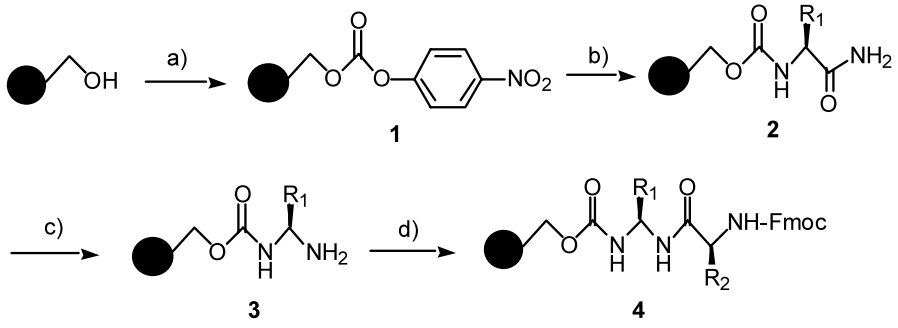
Abstract—Anchoring of an α-amino-acid amide residue by its amine function to a carbamate resin followed by primary amide Hofmann rearrangement led to a *gem*-diamino residue linked to the resin. The generated primary amine could be acylated with various carboxylic compounds offering a large variety of molecules. Furthermore, this new solid-phase strategy allowed a reliable synthesis of a *gem*-diamino monomeric residue which could not be easily obtained in solution due to the limited stability of monocarbamate-protected *gem*-diaminoalkyl derivatives.

Conventional C- to N-terminus solid-phase peptide synthesis is based upon the anchoring of a carboxylic acid to a hydroxy or amino resin. After cleavage from the resin at the end of the synthesis, the peptide could be recovered in the form of an acid or a primary amide. However, the need to prepare a wide variety of low molecular weight compounds on solid support encouraged us to develop a different strategy. For this approach, we investigated the anchoring of amino-acids via their amine function, opening by this way all the chemistry reactions on the free carboxylic acid group. In this paper, we describe the Hofmann rearrangement of a single amino-acid residue anchored to the resin via its amine function. The synthesis of small molecules such as *N*-methylamines,[1] hydantoins,[2] sulfonamides[3] or quinazoline-2.4-diones[4] has already been described via their amine function anchorage. Specific linkers for amines such as triazenes[5,6] were also developed in solid-phase organic chemistry. As far as we know, no publication explored the possibility to anchor amino-acids by their amine function to modify the carboxylic function except Redemann et al.[7] who described α-hydroxy-β-amino-aldehyde syntheses using Dondoni's homologation reaction sequence.[8]

The Hofmann rearrangement reaction of *N*-carbamate-protected single amino-acid residue is not an obvious process in solution due to the instability of the generated *gem*-diamino moiety during work-up. To produce *gem*-diamino derivatives in solution, Hofmann rearrangement was preferentially generated from urethane-protected or acyl-protected dipeptide amides to avoid the formation of unstable geminal diamine amino-acid derivatives. This rearrangement on a monomeric



Scheme 1. *Reagents and conditions*: (a) Cl-COO-pNP, NMM, DCM, 0°C; (b) H_2N-CHR_1-CO-NH_2, DIEA, HOBt·H_2O, DCM/DMF, rt, 12 h; (c) TBIB, pyridine, DMF/H_2O; (d) Fmoc-NH-CHR_2-COOH, BOP, DIEA.

Keywords: Hofmann rearrangement; *gem*-diamino; solid-phase synthesis.

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residue can be achieved on solid support via our strategy (Scheme 1).

To validate this new synthetic pathway, we performed the Hofmann rearrangement on various α-amino-acids (entries 1–7, Table 1). The generated primary amine was then acylated with Fmoc-Phe-OH before cleavage and characterization. When a dipeptide amide was anchored to the resin (entry 8), the *gem*-diamine moiety in position 2 was obtained after the Hofmann rearrangement and the acylation of the generated amine with Fmoc-Ala-OH. Moreover, due to the Hofmann rearrangement, the residue acylating the generated amine was always introduced in the conventional strategy (C- to N-terminus) so classical peptide elongation could be performed. This is exemplified in entry 9, leading after stepwise elongation and cleavage to a tripeptide with a C-terminal *gem*-diamino residue. All crudes were analyzed by reverse phase HPLC and mass spectrometry after cleavage from the support. For all compounds except **8** with an acylated *gem*-diamino moiety, examination of the mass spectra revealed along with the expected MH^+, the presence of a peak at MH^+ minus 17, corresponding to a fragmentation and removal of one molecule of NH_3. This fragmentation of *gem*-diamino peptides has already been reported.[9] Yields and purity were reasonable (Table 1, as a representative HPLC chromatogram of the crudes see Figure 1, entry 4).

The following experimental procedure (entry 1) is representative of all synthesized compounds. The residue was anchored to the resin as an amide. The carbamate resin (1 g, 0.74 mmol) was prepared as previously described[4] and allowed to react overnight with 5 equiv. of H-Leu-NH_2 as its trifluoroacetate salt (900 mg) in

Table 1.

Entry	Starting amide	Product	Yield (%)[a]	MH^+ calcd/exp.	HPLC purity (%) 214/254 nm
1	Leu	Fmoc-Phe-*g*Leu[b]	58	472.25/472.55	84/91
2	Val	Fmoc-Phe-*g*Val[b]	74	458.23/458.53	79/90
3	Ala	Fmoc-Phe-*g*Ala[b]	80	430.21/430.26	71/83
4	Phe	Fmoc-Phe-*g*Phe[b]	65	506.24/506.30	75/71
5	(2Cl-Z)Lys	Fmoc-Phe-*g*(2Cl-Z)Lys[b]	82	655.26/655.31	57/72
6	(Bzl)Ser	Fmoc-Phe-*g*(Bzl)Ser[b]	71	536.25/536.21	79/89
7	(OcHx)Asp	Fmoc-Phe-*g*(OcHx)Asp[b]	48	556.27/556.33	69/85
8	Ala-Phe	Fmoc-Ala-*g*Phe-Ala[c]	54	501.24/501.34	82/80
9	Phe	Fmoc-Phe-Ala-*g*Phe[d]	52	577.27/577.21	73/70

[a] Yields were calculated from the *p*-nitrophenyl carbonate resin substitution.
[b] The generated amine was acylated with Fmoc-Phe-OH.
[c] The generated amine was acylated with Fmoc-Ala-OH.
[d] Two amino-acid residues (Ala, Phe) were stepwise added on the generated amine.

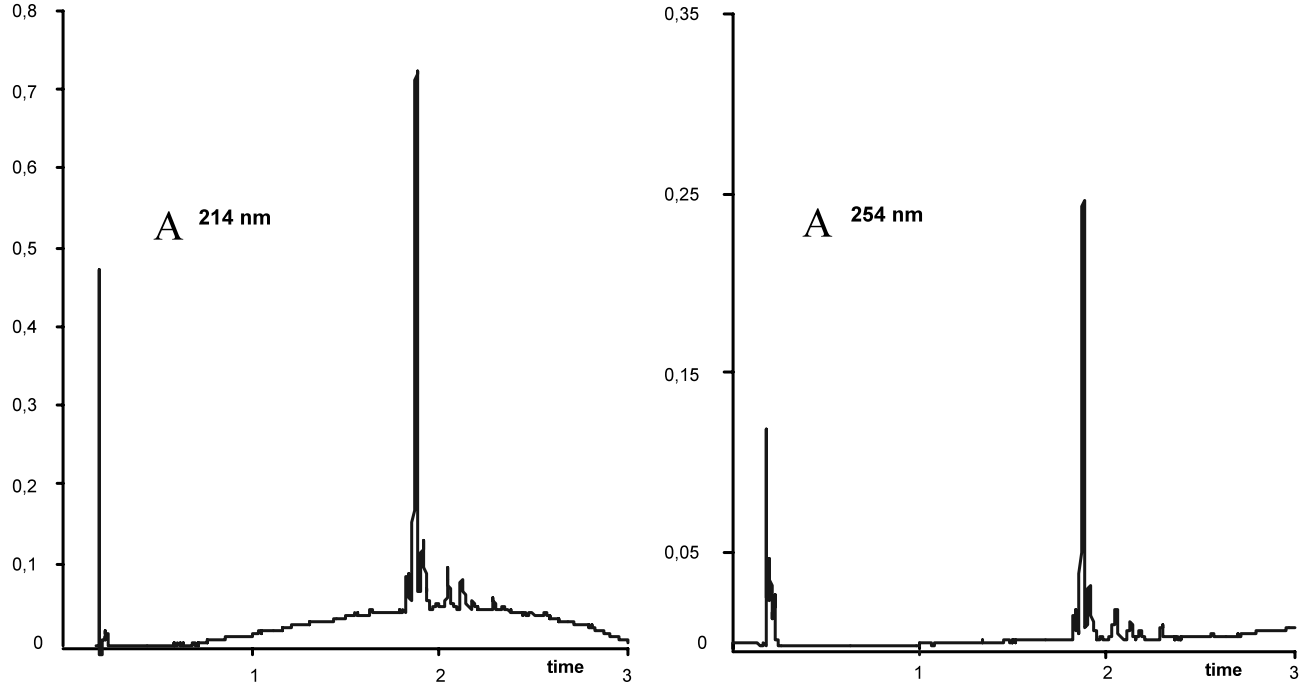

Figure 1. HPLC of the crude **4**.

the presence of 3 equiv. of HOBt (300 mg), 6 equiv. of DIEA (765 μL) in DCM/DMF (50/50). The resin was successively washed with DMF, DCM, MeOH then DMF, DCM and acetylated by a mixture Ac_2O/DCM/Py (45/45/10) in order to cap possible remaining hydroxymethyl groups. After washings (DMF, MeOH, DCM) resin was dried overnight under vacuum. 500 mg of resin (0.375 mmol, 0.75 mmol/g) were solvated in a mixture of 10 mL DMF/H_2O (80/20) with pyridine (10 equiv., 302 μL) and BTIB (bistrifluoroacetoxy iodobenzene) (323 mg, 2 equiv.) and stirred for 1 h. The resin was then washed with DMF and DCM. Fmoc-Phe-OH (5 equiv., 724 mg), BOP (5 equiv., 829 mg) and DIEA (6 equiv., 387 μL) were added to the resin solvated in DMF. After 1 h and classical washings, cleavage from the support was performed by a mixture TFA/DCM (75/25) for 1 h and the crudes analyzed.

In conclusion, we explored anchoring of amino-acid residues by their amine function on solid support followed by Hofmann rearrangement that led to the synthesis of *gem*-diamino residues of amino-acid derivatives. Chemistry on these *gem*-diamino compounds was performed in reasonable yield and purity. *gem*-Diamino containing peptides were obtained on solid support. Further chemistry on these derivatives is under development in this laboratory.

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