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Short Communication

Synthesis of Chiral α-Amino Aldehydes Linked by their Amine Function to Solid Support

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Abstract: The anchoring of an α-amino-acid derivative by its amine function on to a solid support allows some chemical reactions starting from the carboxylic acid function. This paper describes the preparation of α-amino aldehydes linked to the support by their amine function. This was performed by reduction with $LiAlH_4$ of the corresponding Weinreb amide linked to the resin. The aldehydes obtained were then involved in Wittig or reductive amination reactions. In addition, the linked Weinreb amide was reacted with methylmagnesium bromide to yield the corresponding ketone. After cleavage from the support, the compounds were obtained in good to excellent yields and characterized.

Keywords: α-amino aldehyde; Weinreb amide; α-amino ketone; solid phase synthesis; reductive amination

α-Amino aldehydes are important compounds widely used in peptide and organic syntheses. They also provide interesting access to a number of unusual amino acids of biological interest, such as statine and norstatine, and they are key intermediates for the synthesis of pseudopeptide bonds (reduced, carba-, hydroxyethylene peptide bonds, etc...). The two-step procedure, involving the transformation of N-protected α-amino acids to Weinreb amides followed by $LiAlH_4$ reduction, is a reliable method for the preparation of N-protected α-amino aldehydes [1,2]. The reduction proceeds through a stable lithium chelated intermediate avoiding overreduction of the aldehydes to the corresponding alcohols. An 'inverse linkage' of α-amino residues was developed recently [3,4]. This strategy was not chosen to synthesize peptides from *N* to *C* terminals, but it was explored to generate low molecular weight molecules from α-amino acid derivatives. This study demonstrated that α-amino aldehydes can be generated on a solid support via a carbamate linker on the Wang resin. To validate this strategy, the prepared aldehydes were allowed to react (1) with amines in reductive amination conditions to yield 'reduced bonds' and (2) with phosphoranes to yield 'ethylene bonds'.

For this purpose, protected amino acid residues were anchored to the resin as Weinreb amides on a carbamate resin prepared as described previously [5] and their reduction into aldehydes was optimized on a solid support (Scheme 1). To date, to our knowledge, no α-amino-linked aldehyde synthesis has been described on a solid support

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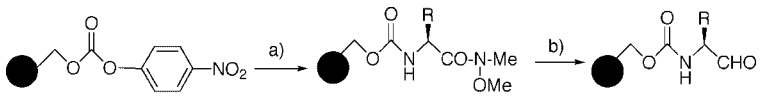
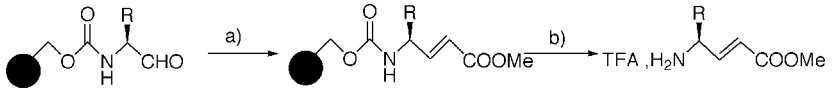
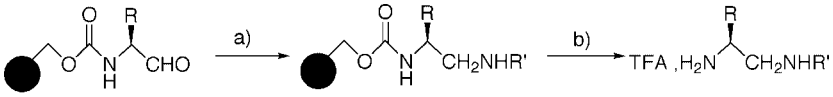


Scheme 1 Synthesis of α-amino aldehydes linked by their amino function to the solid support.



Scheme 2 Wittig reaction on supported aldehydes.



Scheme 3 Reductive amination on supported aldehydes.

from Weinreb amides. The supported reduction of Weinreb amide on Asp and Glu side-chains to generate lipidic residues was reported recently [6]. Redemann *et al.* described α-hydroxy-β-amino-aldehyde syntheses using Dondoni's homologation reaction sequence on Weinreb amides of α-amino acids linked to a polymer-bound Boc-linker [7]. Porco *et al.* automated the addition of Grignard reagents to Weinreb amide derivatives on Argo-Gel-Wang resin to yield ketones [8]. Gosselin *et al.* developed the synthesis of alaninal on non-cross-linked polystyrene from the corresponding isoxazolidide to prepare enantiopure norephedrines [9]. Finally, Dolle *et al.* reported Wittig-Horner reactions of resin-bound N-acyl amino acid aldehydes by oxydation of β-amino alcohols [10].

To validate our strategy, H-Phe-N(Me)OMe was anchored as a carbamate to the Wang resin and the Weinreb amide was reduced in THF at 0 °C. It was found that 6 eq of hydride for 40 min was necessary to complete the reaction. α-Amino aldehydes are not optically stable and it was difficult to release them from the support. To first demonstrate that the linked aldehyde moiety had been generated it was allowed to react with the stable, commercially available carbomethoxymethylene triphenylphosphorane in excess (6 eq.) in anhydrous DMF for 3 h at 75 °C (Scheme 2). The resin was then filtered, washed successively with MeOH and DCM and dried *in vacuo*. The compound was then classically cleaved from the support in acidic conditions (TFA/DCM: 75/25, v/v) for 1 h. The solvents were concentrated and the residue was dissolved in CH_3CN/H_2O/TFA (50/50/0.1, v/v/v/) before lyophilization and analyses. The crude HPLC chromatogram revealed the presence of a major compound integrating for 92% at 214 nm. It was purified (yield 86% from the *p*-nitrophenyl carbonate resin substitution) and identified by mass spectrometry $[M+H]^+$: 206.1, and ^1H NMR spectroscopy. Coupling constants ($J = 15.9$ Hz) revealed a total *trans*-configuration of the double bond.

The same linked aldehyde was reacted with 10 eq. of methyl magnesium bromide (3M in diethyl ether) in THF. After 1 h, conversion was found to be 93% (cleavage of a resin aliquot) and was quantitative after 12 h. Analysis by LC-MS provided the mass of the expected ketone $[M+H]^+$: 164.3.

In a second set of experiments, the generated linked aldehydes (Phe, Ala, Leu, Val, Lys) were allowed to react with various amines (Figure 1) (5 eq.) in the presence of sodium cyanoborohydride (10 eq.) in DMF/AcOH (97/3, v/v) as solvent (Scheme 3 and Table 1). Release of the obtained compounds from the support by acidic treatment gave compounds in yields between 80% and 85% (calculated from the *p*-nitrophenyl carbonate resin substitution). All compounds were analysed by RP-HPLC and mass spectrometry. Furthermore, examination of the ^1H NMR spectrum of crude compound **2f** did not detect any epimerization within the limits of ^1H NMR detection.

In conclusion, it was demonstrated that the generation of supported α-amino aldehydes was

Table 1 HPLC Purity of Crude Compounds at 214 nm

Compound	Aldehyde	Amine	RT (min)[a]	HPLC purity (214 nm)	MW calculated	m/z ($[M+H]^+$) experimental
1	**Phe**	a	1.087	**81**	240.2	241.1
		b	1.083	**89**	297.2	298.2
		c	1.462	**81**	330.2	331.2
		d	1.135	**58**	270.2	271.3
		e	1.281	**53**	268.2	269.2
2	**Ala**	a	0.694	**91**	164.1	165.1
		b	0.762	**83**	221.2	222.1
		c	1.238	**80**	254.2	255.4
		d	0.817	**79**	194.1	195.3
		e	0.985	**69**	192.2	193.2
		f	0.973	**100**	236.1	237.1
3	**Leu**	a	0.979	**92**	206.2	207.0
		c	1.381	**83**	296.2	297.2
		d	1.033	**83**	236.2	237.2
		e	1.173	**58**	234.4	235.3
		f	1.028	**100**	278.2	279.3
4	**Val**	f	0.898	**89**	264.2	265.1
5	**Lys(2Cl-Z)**	b	1.421	**69**	446.2	447.4

[a] Chromolith SpeedROD column (50 × 4.6 mm), flow rate 5 ml/min, gradient from H_2O/TFA, 0.1% to CH_3CN/TFA, 0.1% in 3 min.

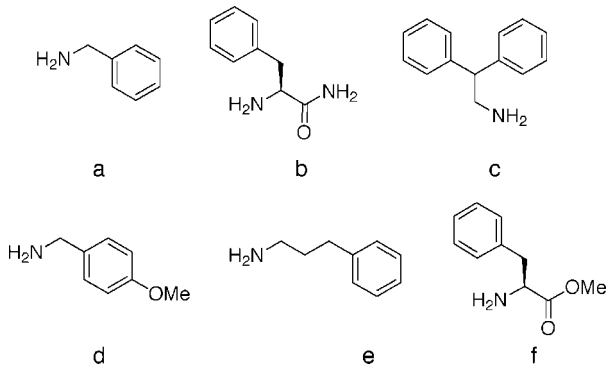


Figure 1 Amines involved in the reductive amination.

possible by inverse anchoring. Generation and work-up of these aldehydes were easy on the solid support. They were obtained in high purity and allowed various reactions in good to high yields.

General Procedure for Generation of the Aldehyde Moiety

The Weinreb amides of N-protected α-amino acids were prepared in solution and after deprotection of the amine function were anchored as a carbamate to the Wang resin which had been previously activated by the *p*-nitrophenyl chloroformate [5]. Weinreb amides were reduced in THF at 0 °C with 6 eq. of hydride (1.25 eq. $AlLiH_4$) for 40 min (in the case of 2Cl-Z-Lys, 2 eq. of hydride was added, due to the side-chain protection). Reaction mixtures were then hydrolysed with a 1 M $KHSO_4$ solution. After filtration, resins were washed successively with a saturated $NaHCO_3$ solution, water, MeOH, DMF and CH_2Cl_2 and involved in the next reaction step.

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